

Evolving Frontline ALL Therapies Incorporating Novel TKIs and Immune Therapies

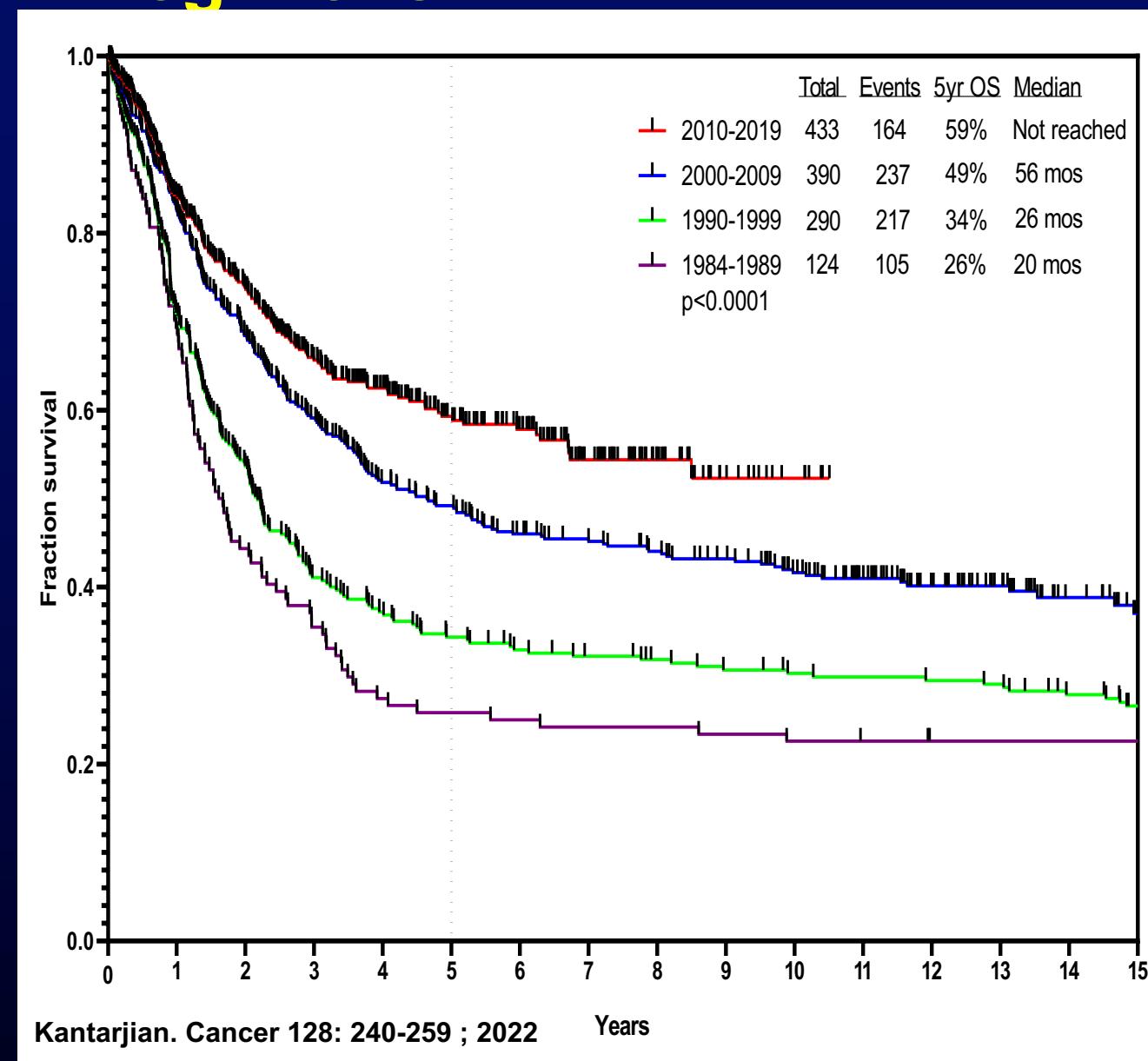
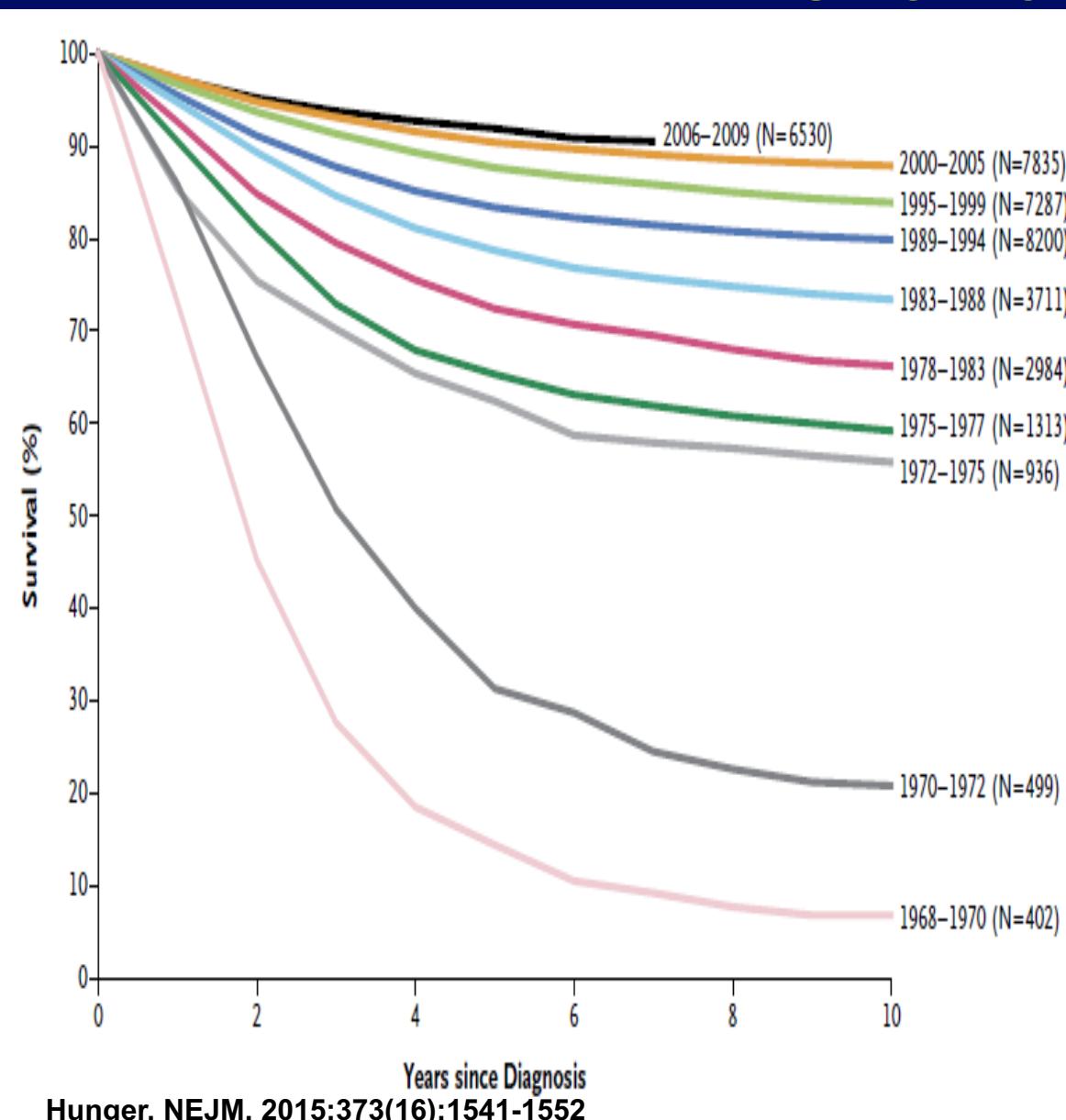
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Emory Sea Island (my favorite) Meeting; July 2024

Conflict of Interest Disclosure

- **Research Grants**
 - Ascentage, Pfizer, Takeda, Amgen, AbbVie
- **Consultancy and advisory roles**
 - Pfizer, Takeda, Amgen, AbbVie, BMS, Ascentage

Survival in Pediatric and Adult ALL with Classical Intensive ChemoRx Regimens



Adult ALL Rx – Why Should it Change?

- Too much chemoRx (15 drugs) for too long (3 years of intensive induction, consolidation, intensification, maintenance)
- Manageable in leukemia centers, cooperative groups; not in community practice, rural areas, emerging nations
- Childhood ALL in India : Cure rate 80% if wealthy (2%), 40-50% if middle class (15-20%), 10% if poor (70+%)
- Can we develop shorter less chemo-intensive regimens that incorporate the more effective Rxs, and which are available and affordable to all?
- Goal/dream-- Dose-dense miniCVD-INO-BLINA 6 months; +/- CARTs

What Should We Incorporate?

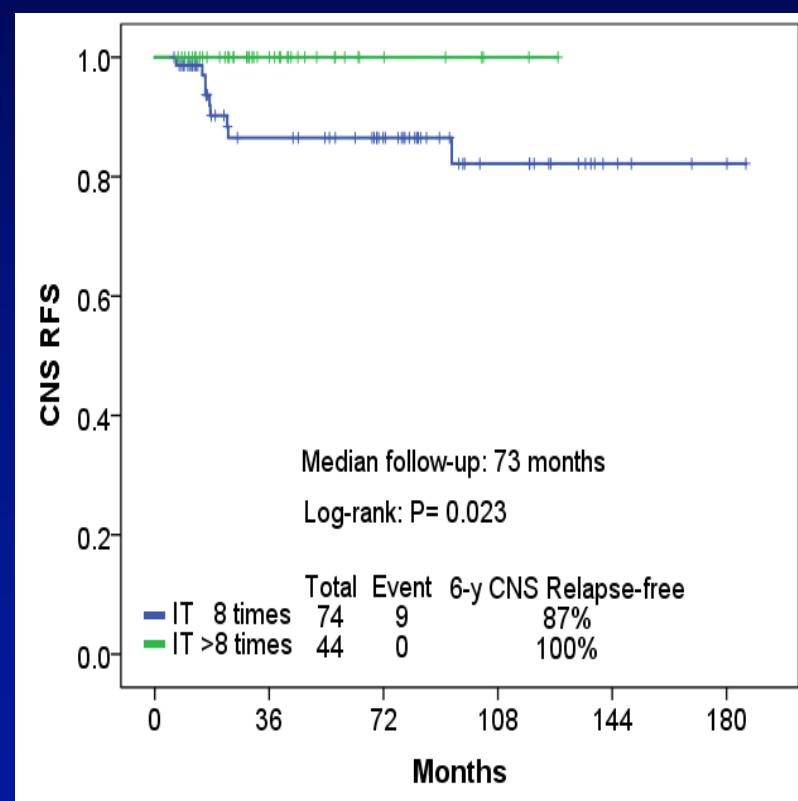
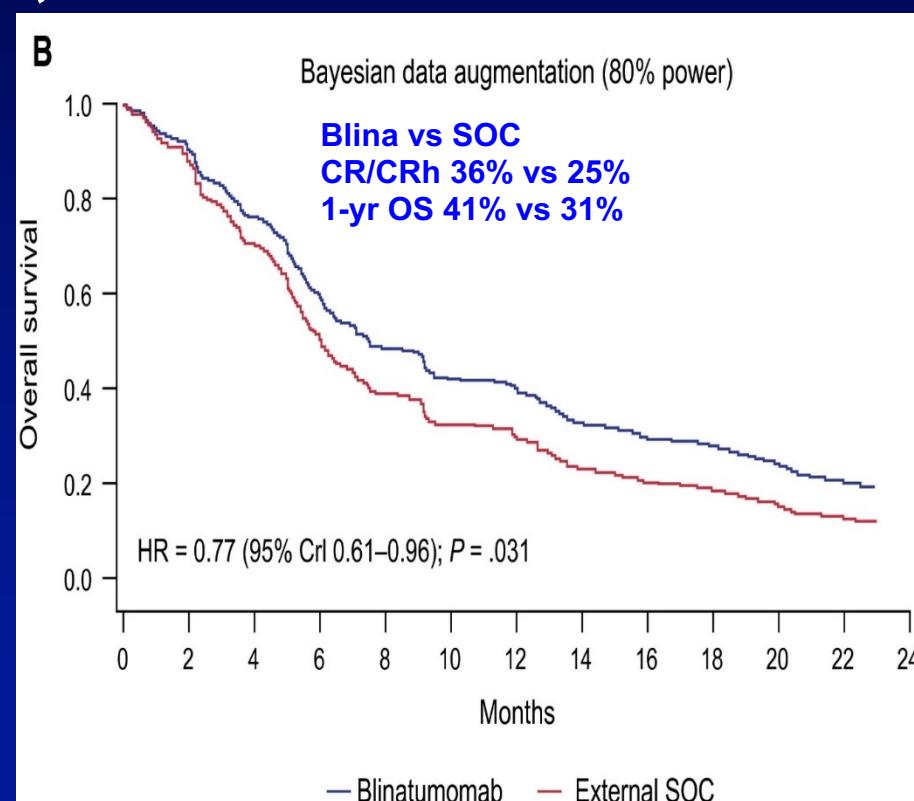
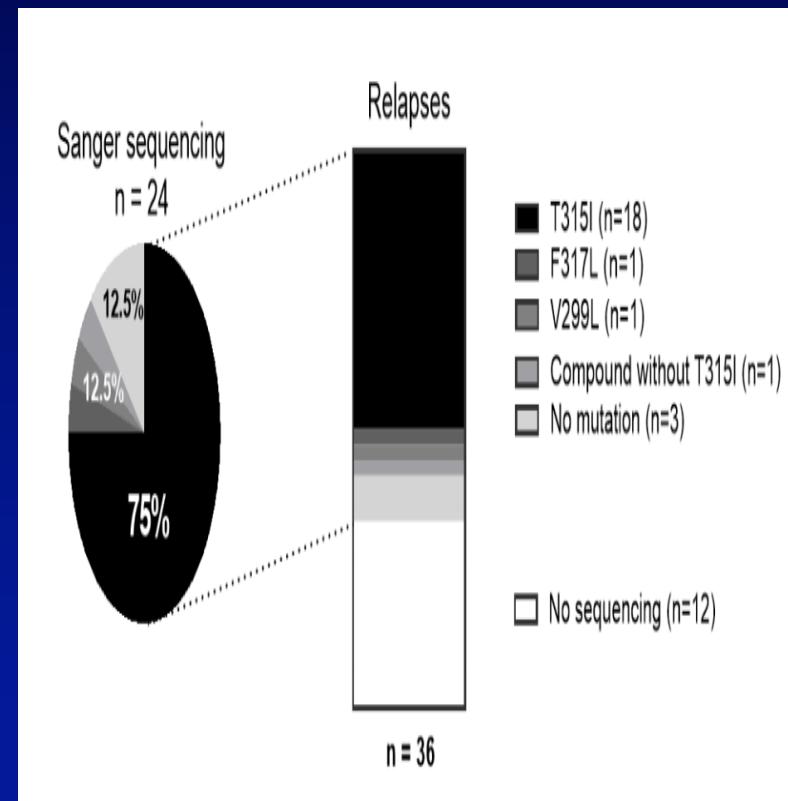
- Ph-positive ALL -- Ponatinib, blinatumomab. Novel BCR::ABL1 TKIs (asciminib; olverembinib)
- Pre-B ALL -- Antibodies targeting CD19 (blinatumomab), CD22 (inotuzumab), and CD20 antibodies (rituximab, CD20 BiTEs)
- CARTs consolidation instead of allo SCT??
- MRD tracking by NGS clonoseq for IgHV– (analyzes >1 million cells) to decide on changes in Rx, and duration of Rx
- Dose-dense mini-CVD-inotuzumab-blinatumomab +/-CARTs regimen –7 months of Rx
- T-ALL – Need CD7 CARTs

Evolution of Ph-positive ALL Research and Rx at MDACC (1992-2022)

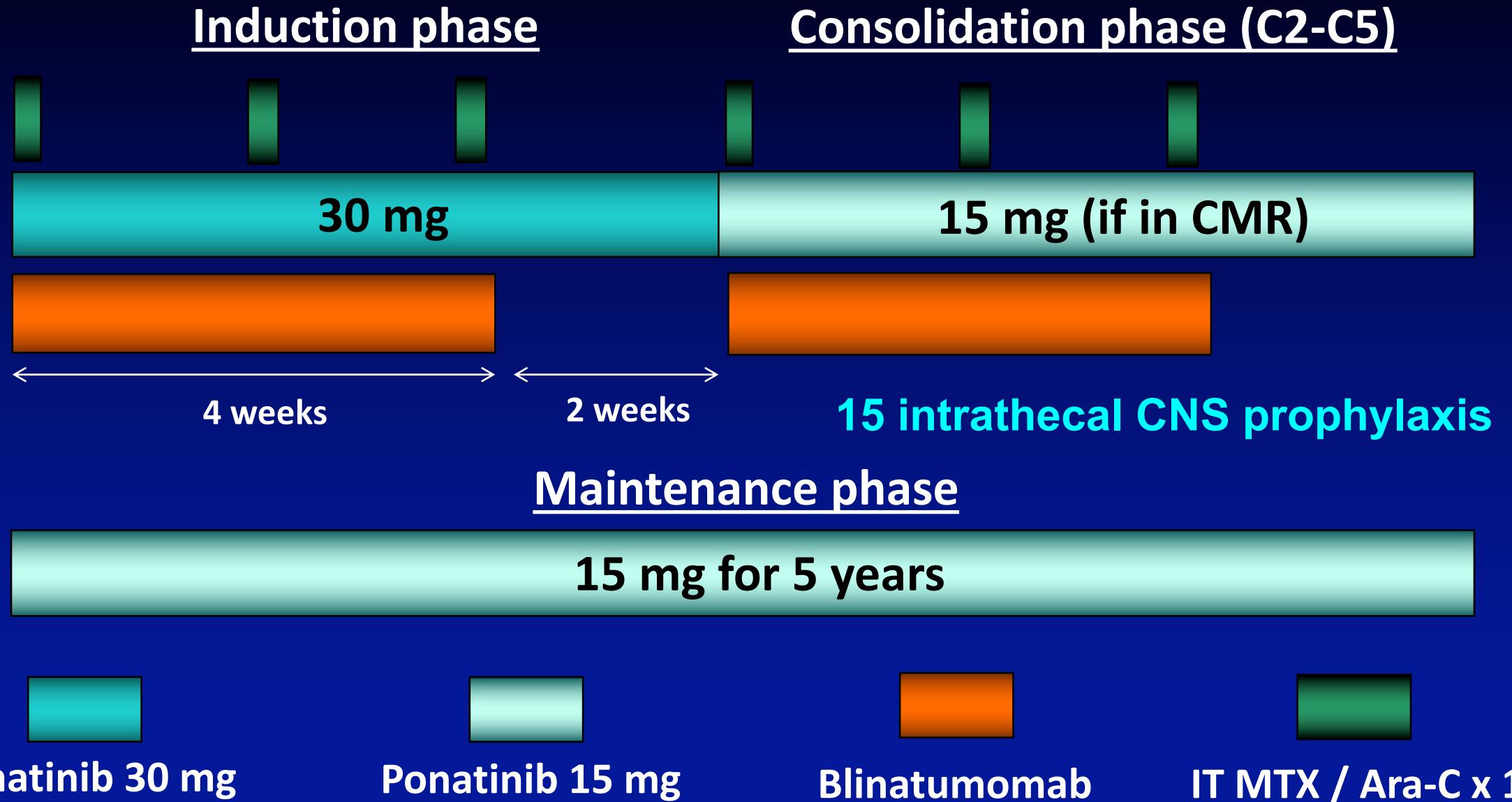
- 1992 -- Hyper-CVAD; 8 IT; allo SCT when possible
- 2000 -- Hyper-CVAD + imatinib; 8 IT; allo SCT in CR
- 2006 – Hyper-CVAD + dasatinib; 8 IT; allo SCT in CR if no CMR by 3+ mos
- 2010 – Hyper-CVAD + ponatinib; 12 IT; allo SCT less and only if no MMR by 3+ mos
- 2017 – Ponatinib dose-response adjusted + blinatumomab; 12-15 IT; allo SCT rare

Ph-Positive ALL – Rationale for Changes

- 75% of relapses with T315I mutation = ponatinib
- Blinatumomab better than intensive chemoRx = blinatumomab replaces chemoRx and reduces need for allo SCT
- More CNS relapses with longer survival, and after elimination of HD araC = increase ITs from 8 to 12, and now to 15



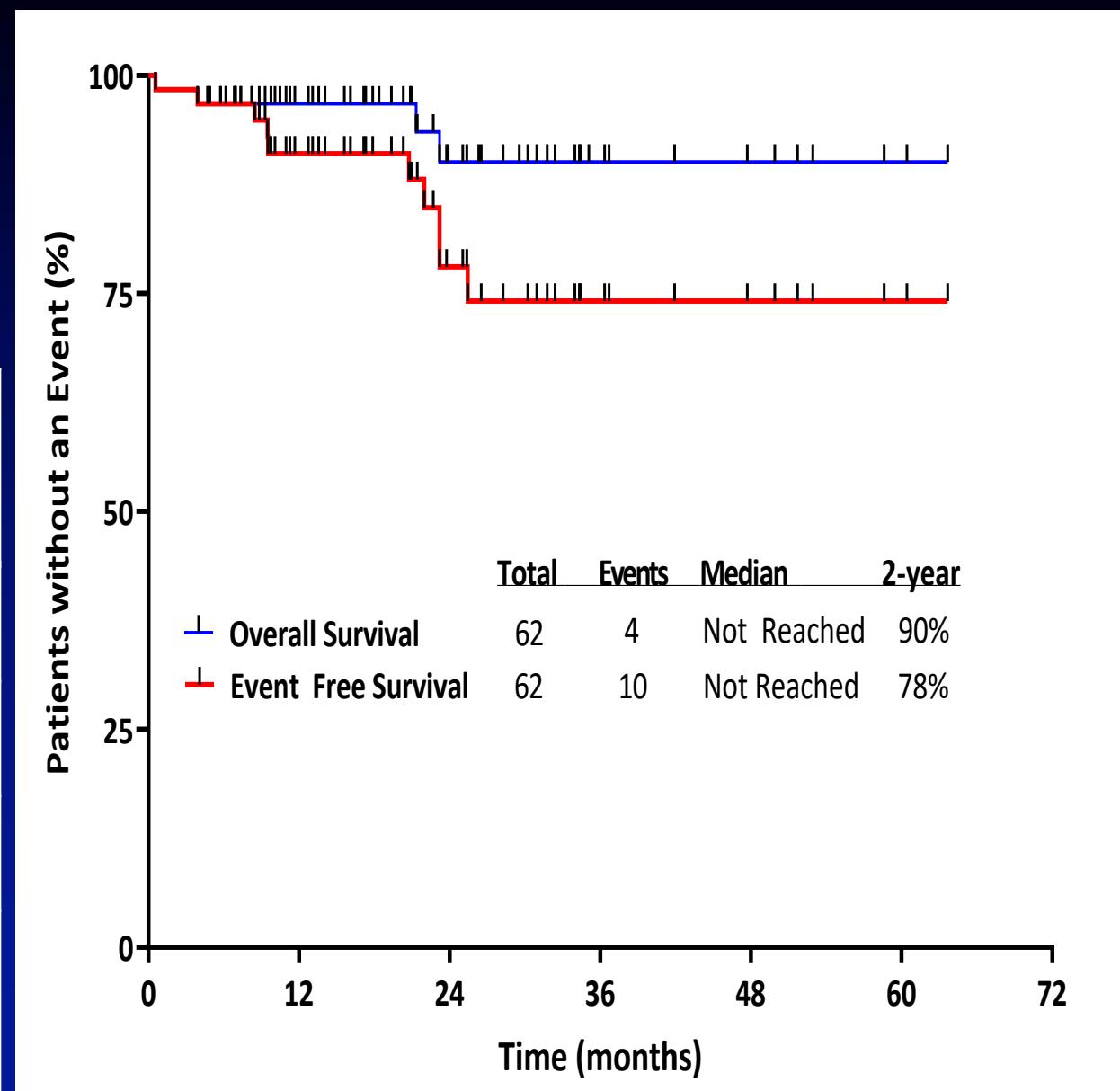
Ponatinib + Blinatumomab in Ph+ ALL: Regimen



Ponatinib and Blinatumomab in Newly Dx Ph-Positive ALL

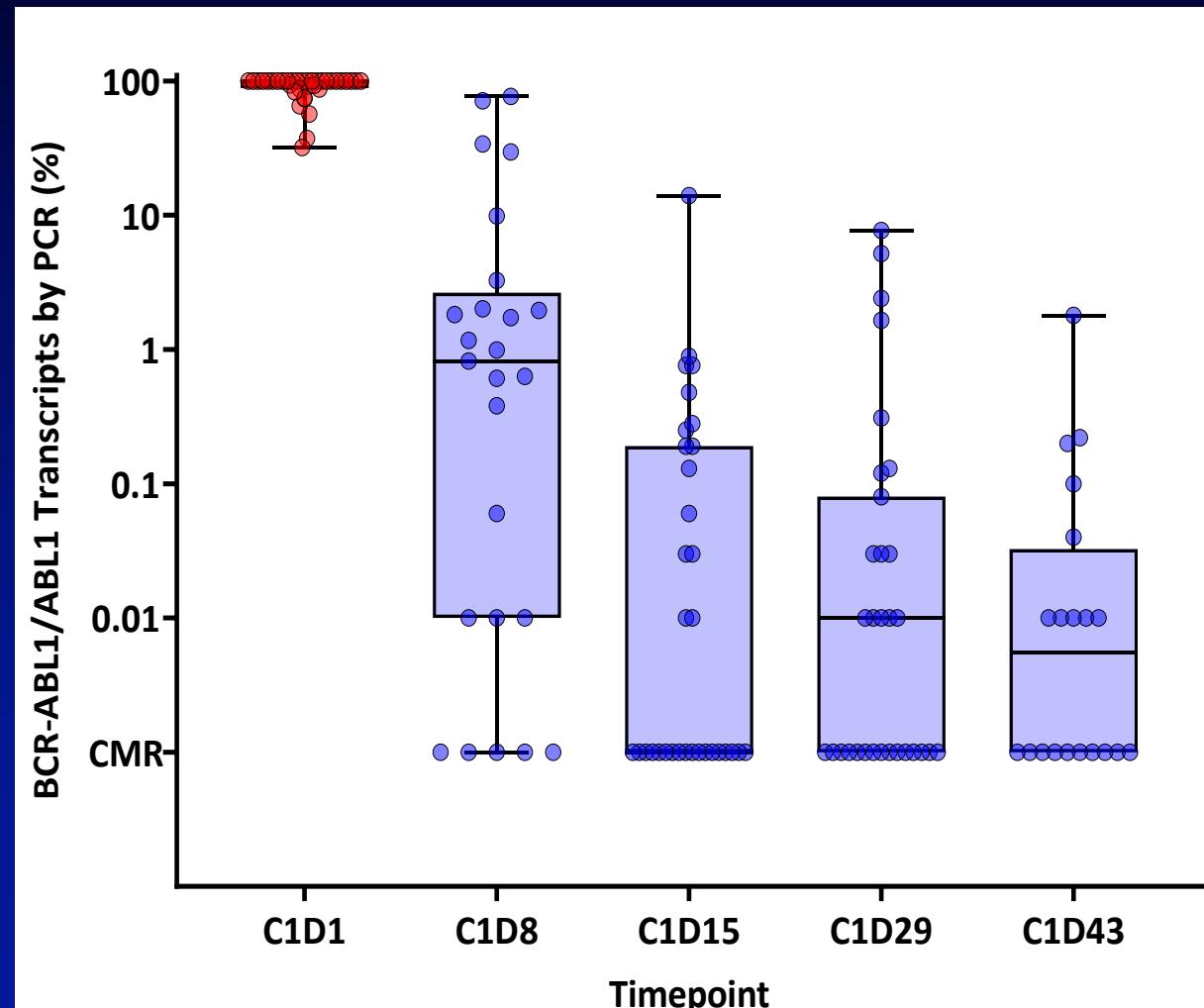
- 62 pts Rx with simultaneous ponatinib 30-15mg/D and blinatumomab x 5 courses. 12-15 ITs
- Only 1 pt had SCT(2%)
- Median F/U 19 months. 2-yr EFS 78%, OS 89%
- 7 relapses (all p190): 4 CNS, 1 CRLF2+ (Ph-), 2 systemic

Parameter	%
CR-CRi	98
% CMR	84
% NGS-MRD negative	91
% 2-yr OS	89

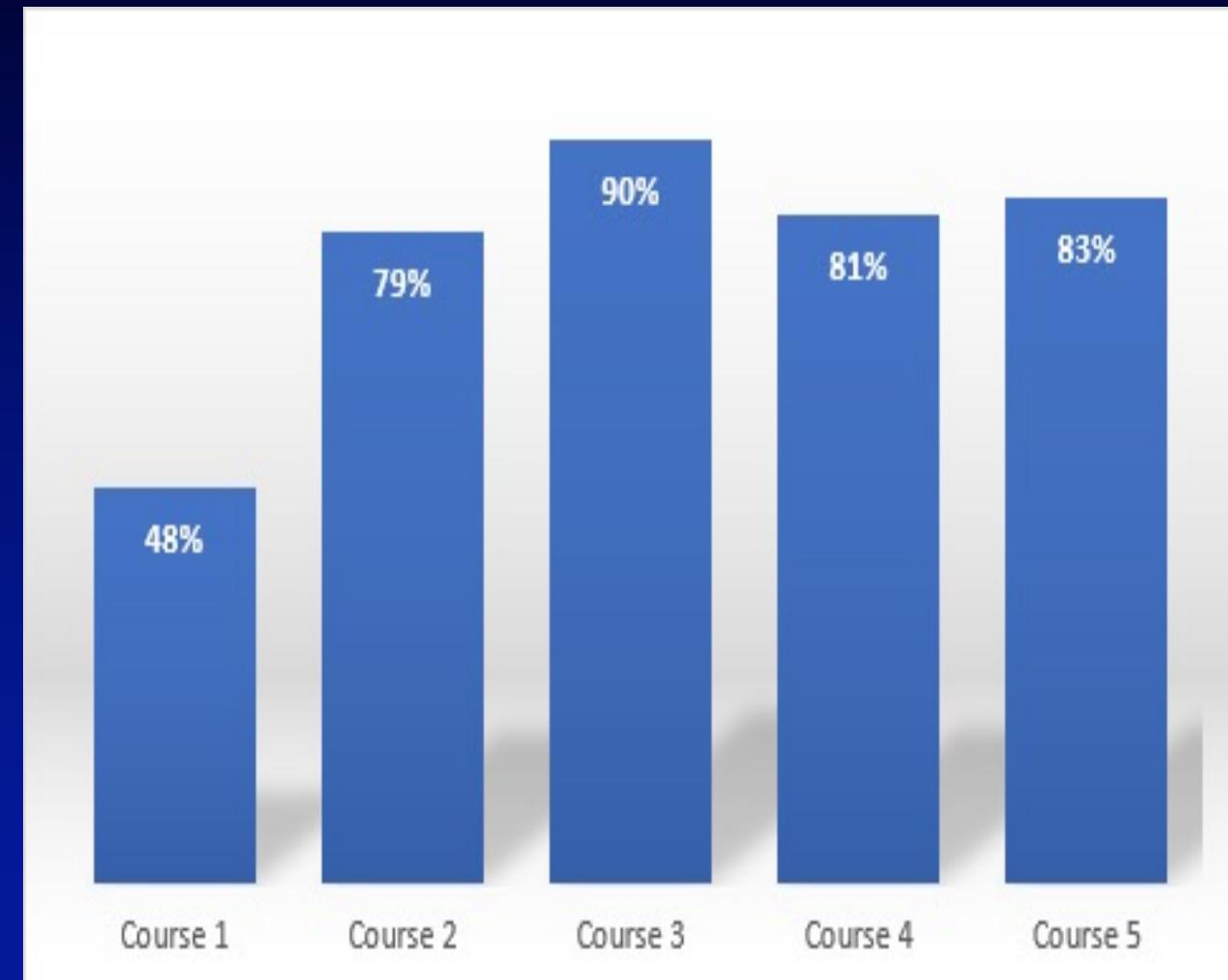


Ponatinib and Blinatumomab in Newly Dx Ph-Positive ALL. Dynamic of Molecular Response

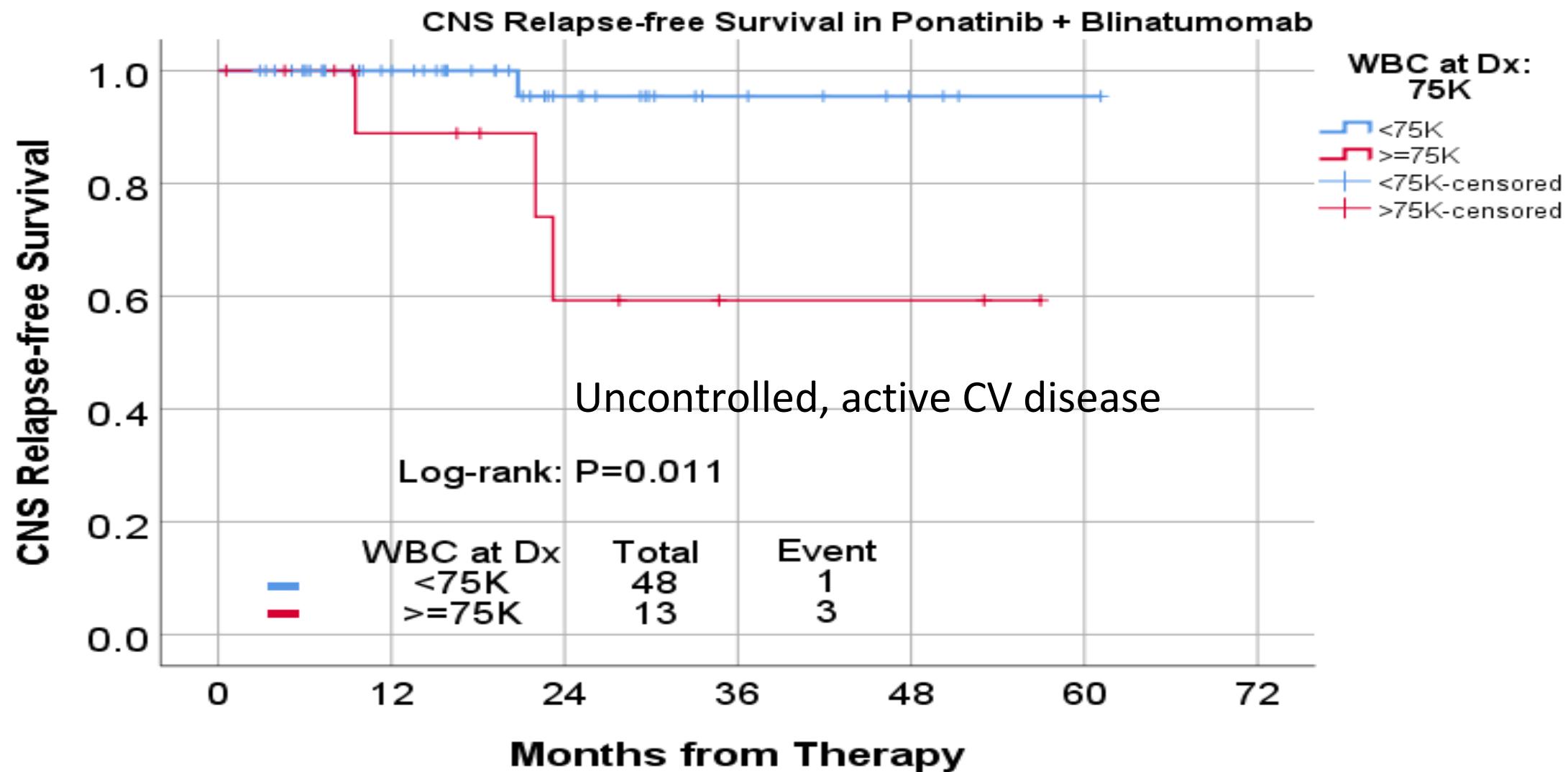
By RT-PCR



By NGS



Ponatinib + Blinatumomab in Ph+ ALL. CNS Relapses

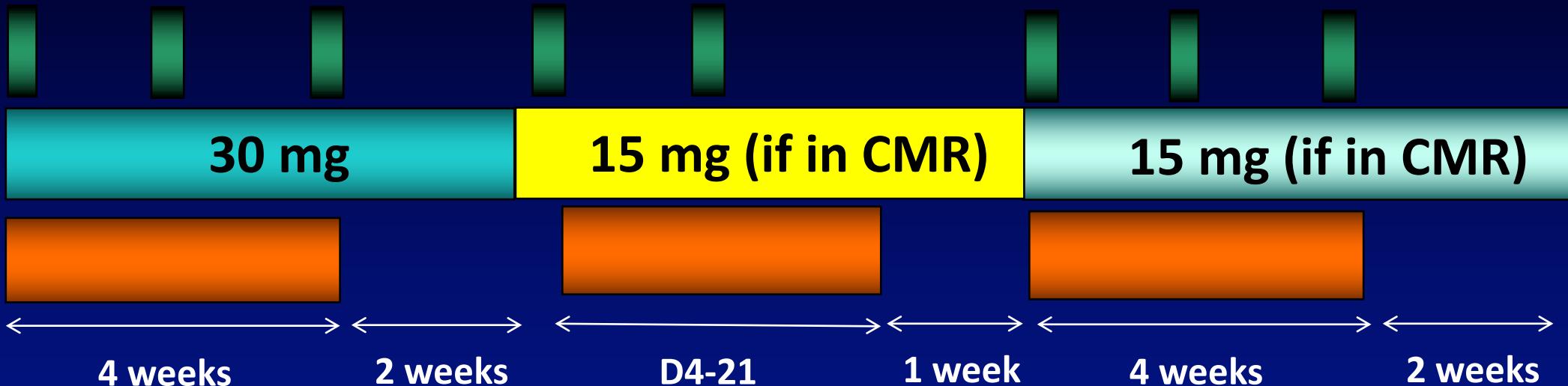


- By MVA, high WBC only predictive for CNS relapses (OR=10.3; p=0.047)

Ponatinib + Blinatumomab in Ph+ ALL. Regimen

(WBC \geq 75K)

Induction phase (C1-2) Systemic RX (C3-4) Consolidation phase (C5-C6)



Maintenance phase

15 mg for 5 years



Ponatinib 30 mg



Ponatinib 15 mg



HDAC/MTX

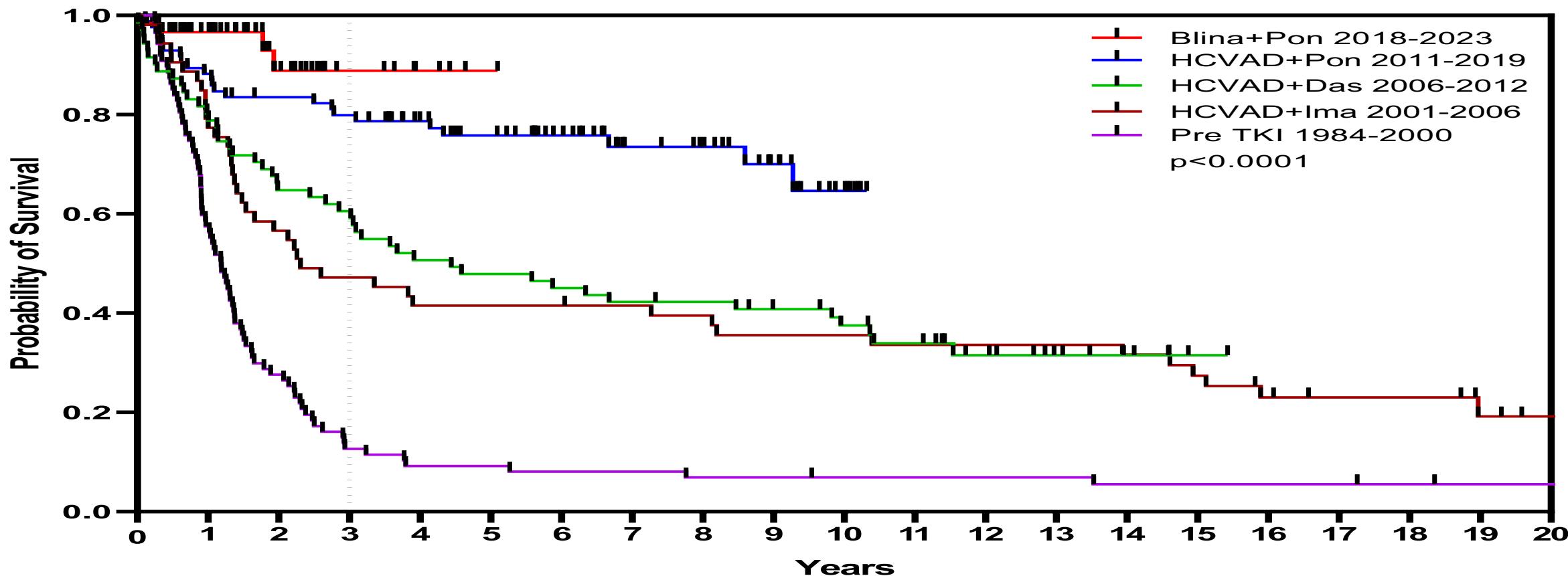


Blinatumomab



IT MTX / Ara-C x 15

Ph+ ALL. Survival by Decade (MDACC 1984-2023)

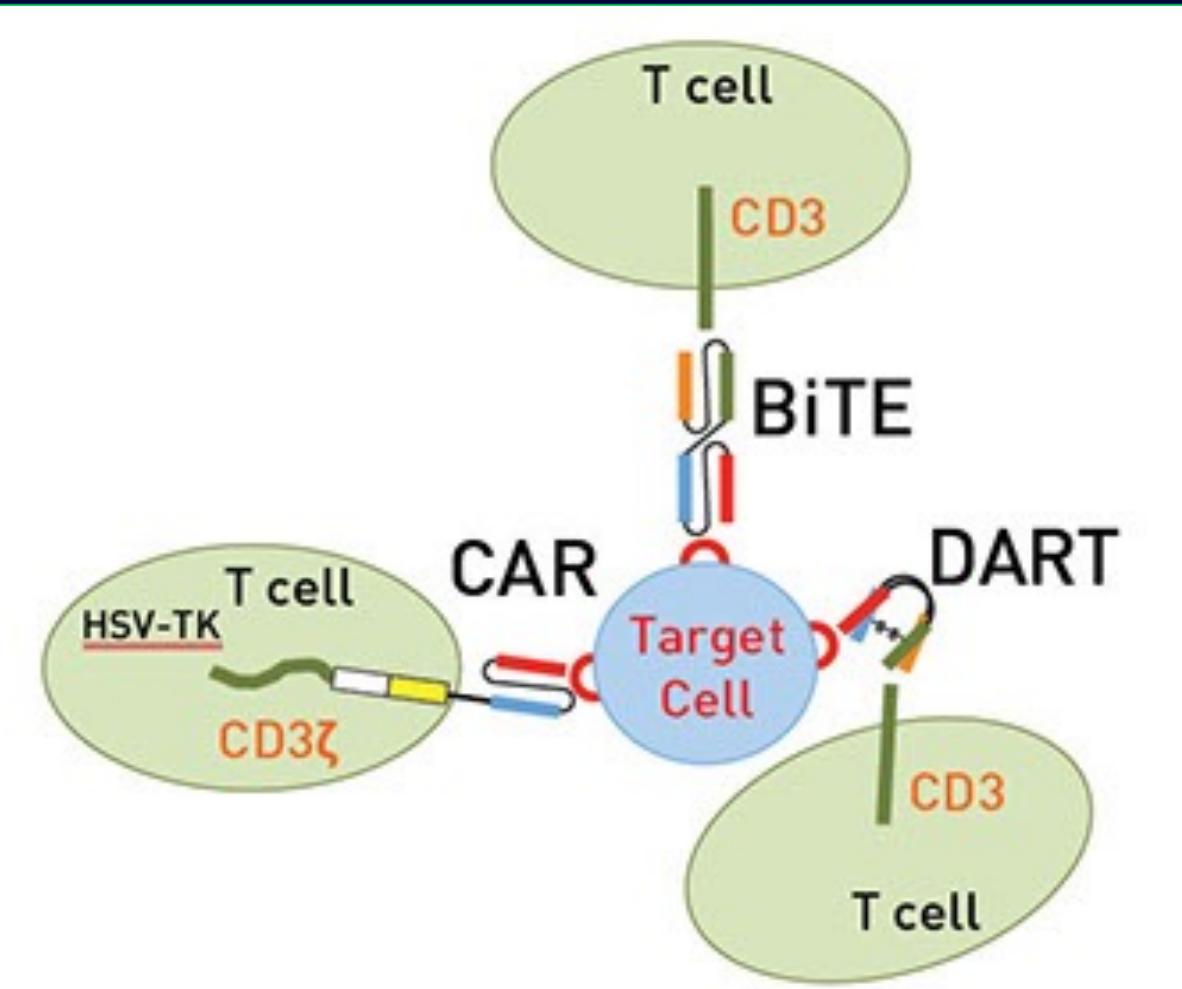
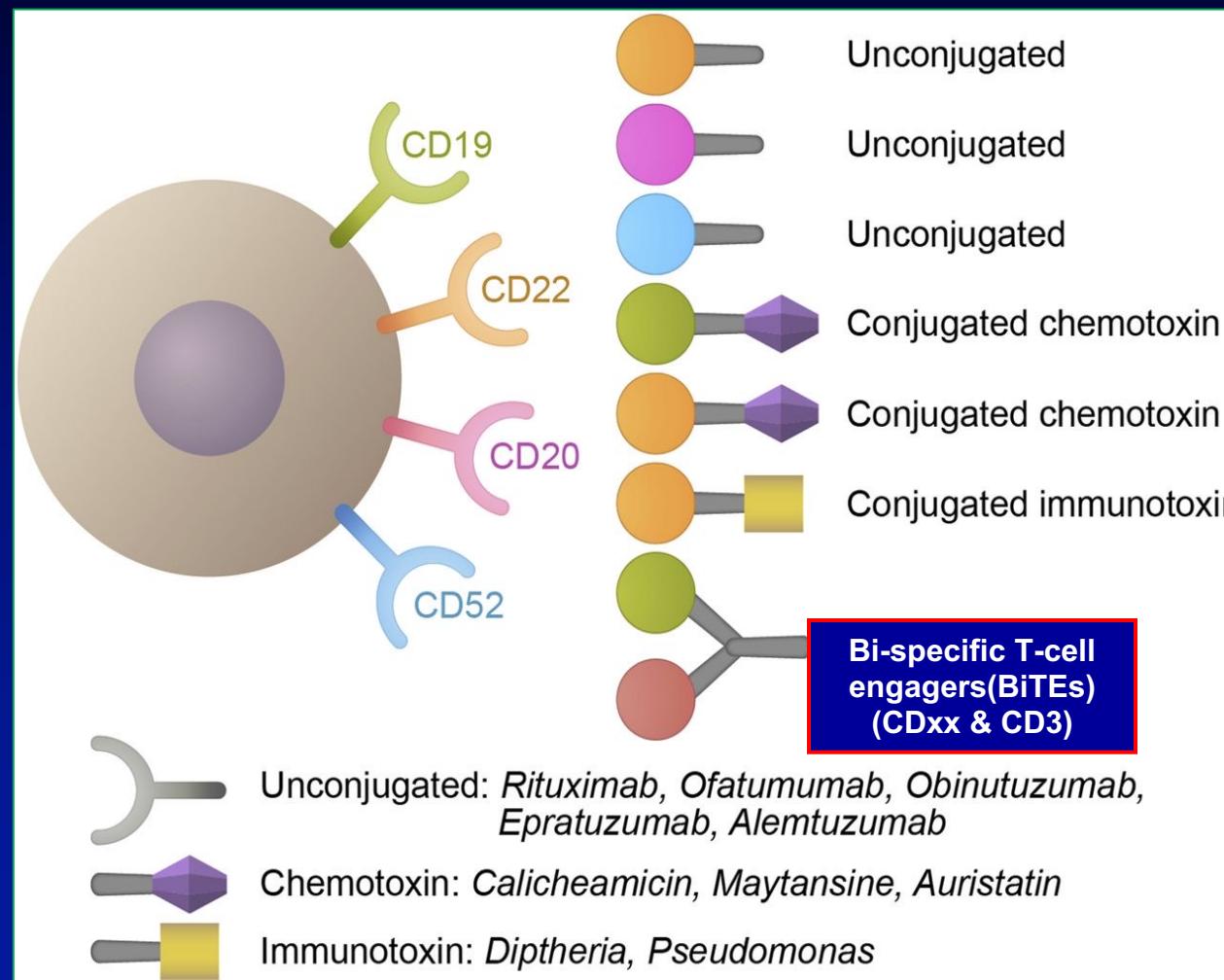


	Total	Events	3yr OS	5yr OS	Median
Blina+Pon 2018-2022	62	4	89%	—	Not reached
HCVAD+Pon 2011-2019	85	23	80%	76%	Not reached
HCVAD+Das 2006-2012	71	47	61%	48%	53 mos
HCVAD+Ima 2001-2006	53	41	47%	42%	28 mos
Pre TKI 1984-2000	87	83	13%	9%	14 mos

$p < 0.0001$

Immuno-oncology in ALL

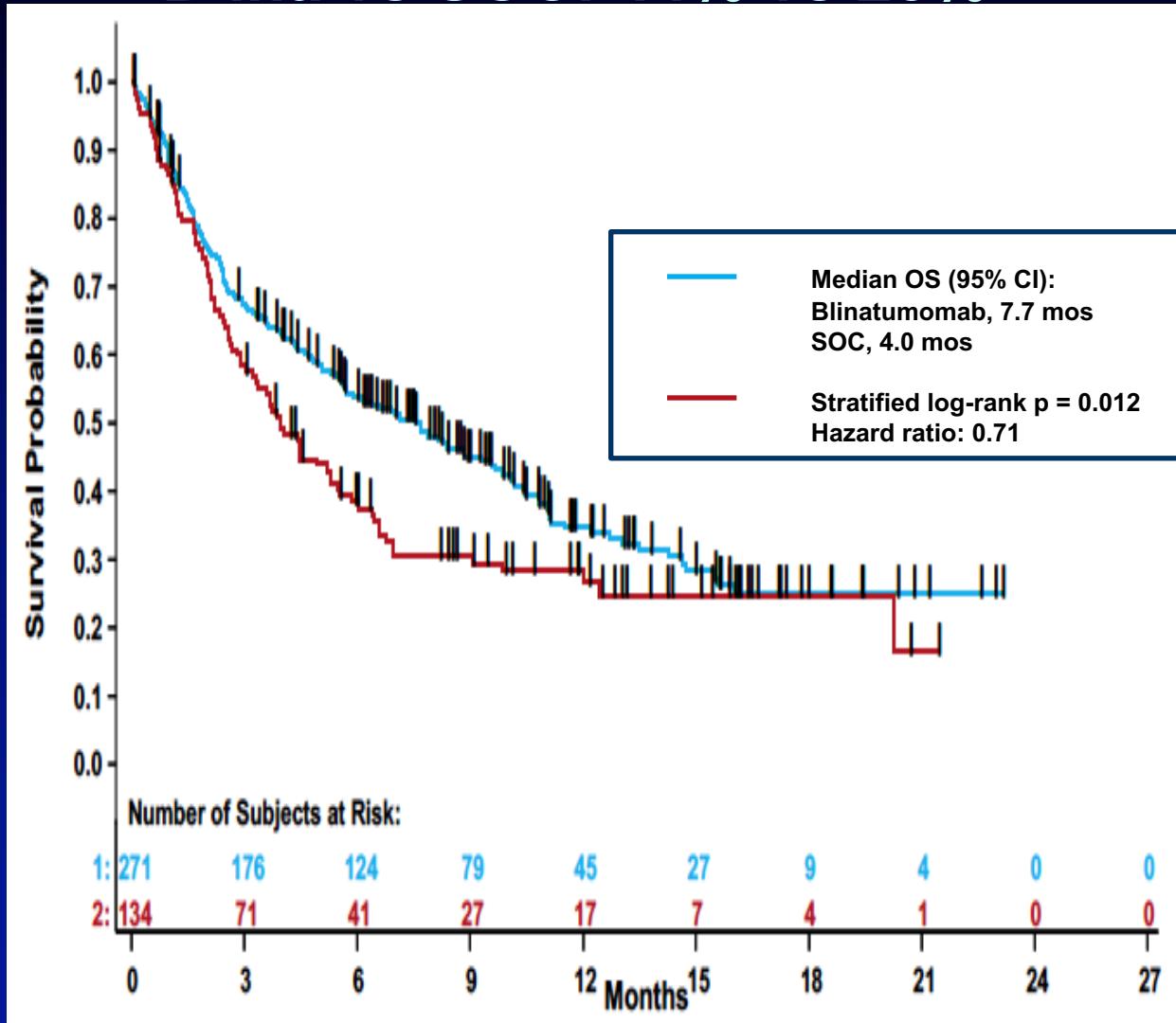
- Antibodies, ADCs, immunotoxins, BiTEs, CARTcells



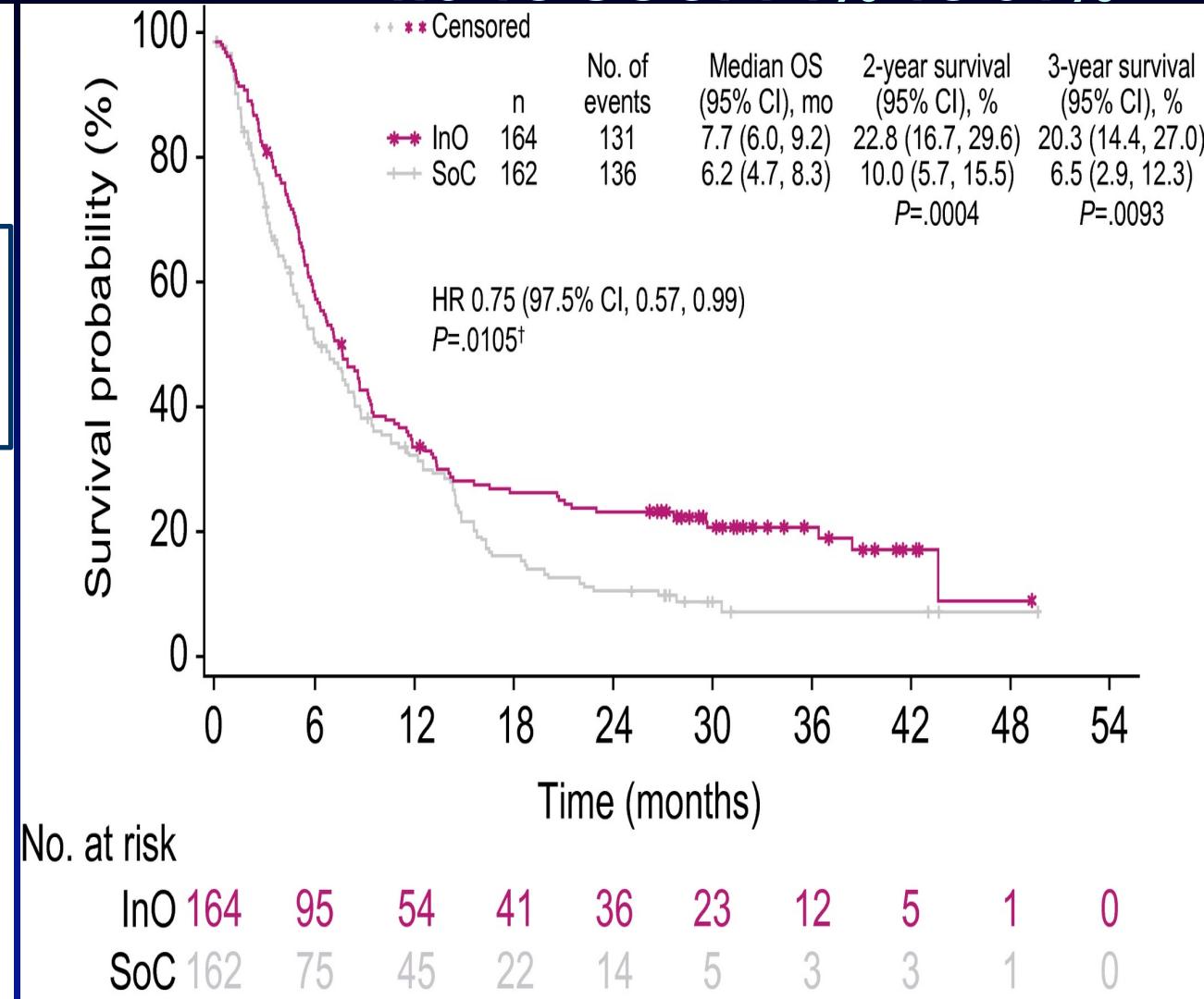
Blinatumomab/Inotuzumab vs ChemoRx in R-R ALL

- Marrow CR

Blina vs SOC: 44% vs 25%

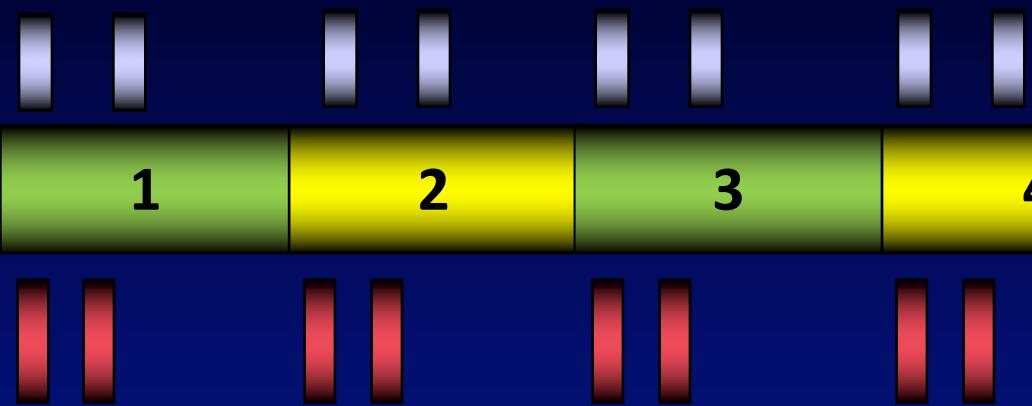


Ino vs SOC: 74% vs 31%



Hyper-CVAD + Blinatumomab in B-ALL: Regimen

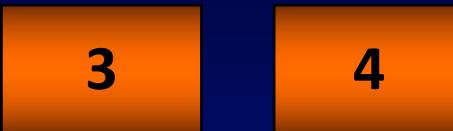
Intensive phase



Blinatumomab phase

*After 2 cycles of chemo for MRD+, Ho-Tr, Ph-like, TP53, t(4;11)

↔
4 wk 2 wk



Maintenance phase



Hyper-CVAD

MTX + Ara-C

Ofatumumab or rituximab

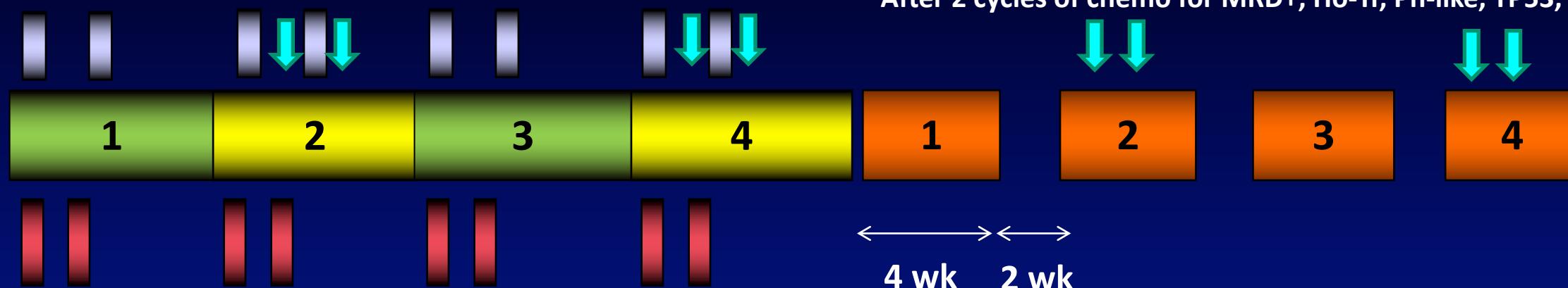
IT MTX / Ara-C x 8

Blinatumomab

POMP

Hyper-CVAD + Blina + InO in B-ALL: Regimen (2nd Cohort)

Intensive phase



Blinatumomab phase

*After 2 cycles of chemo for MRD+, Ho-Tr, Ph-like, TP53, t(4;11)

Maintenance phase



Hyper-CVAD

Ofatumumab or rituximab

Blinatumomab

MTX (500 mg/m²) + Ara-C (1g/m²)

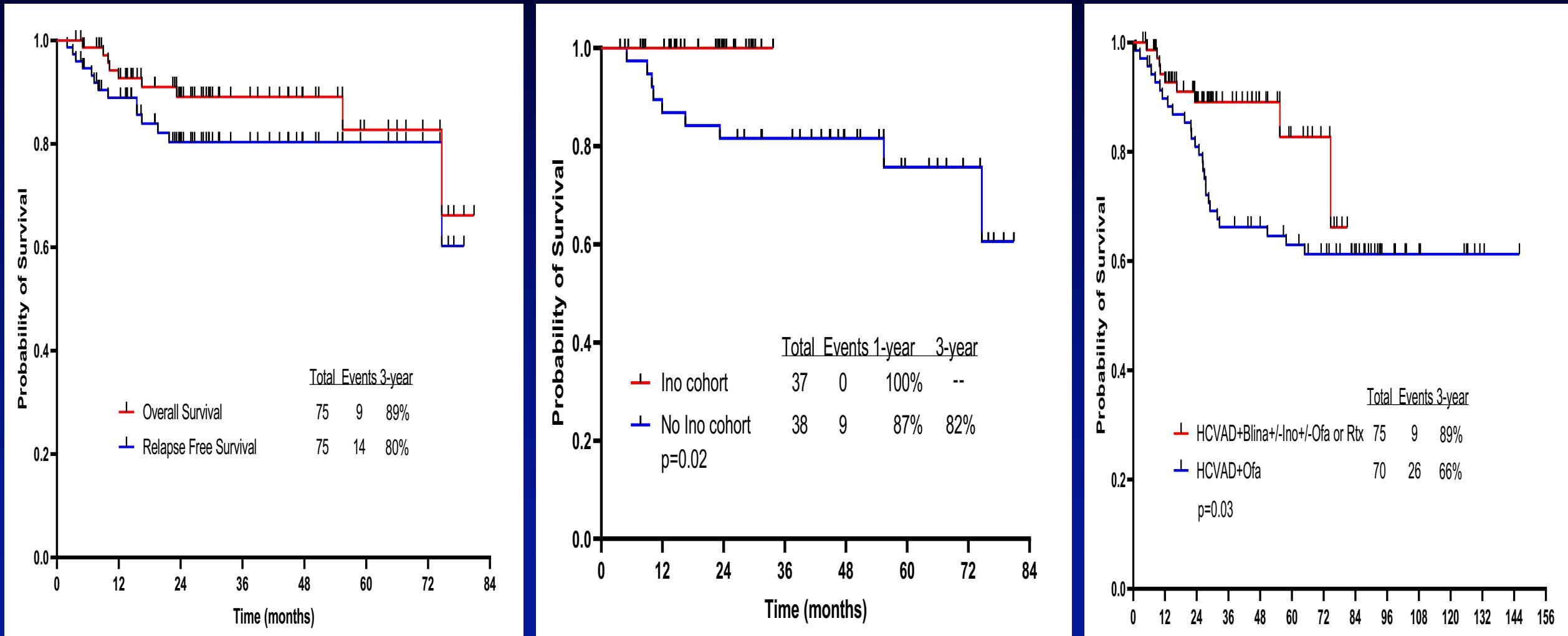
IT MTX/Ara-C x 8

POMP

↓ ↓ Inotuzumab 0.3 mg/m² on D1 and D8

Hyper CVAD-Inotuzumab→Blinatumomab in Newly Dx Adult ALL

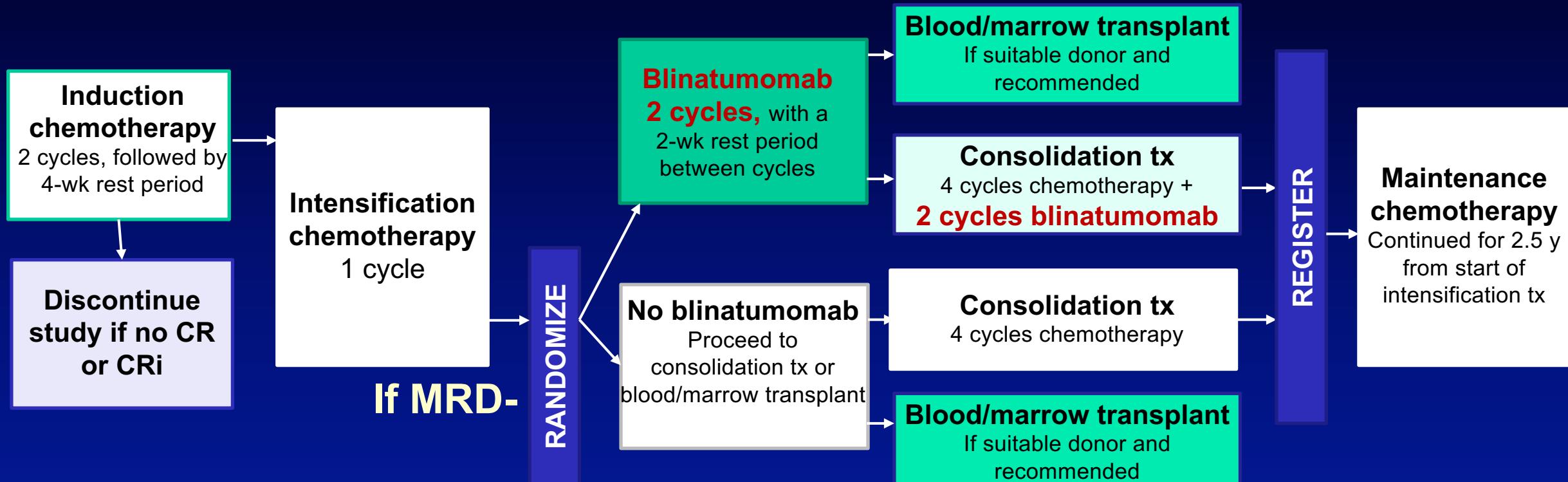
- 75 pts; median age 33 yrs (18-59).
- Rx with O-HCVAD x 4; blinax4→POMP 1 yr with blina Q3 mos; Ino 0.3 mg/m² D1&8 C2,4,6,8 (2.4 mg/m²)
- CR rate 100%; MRD negative 95% (66% at CR); NGS-MRD negative 73%; 60-day mortality 0%; 24 (32%) allo-SCT;



Frontline Blinatumomab and Inotuzumab Combinations in Adult Newly Dx ALL

	Agent	N	Median Age (yrs, range)	% CR	% MRD negativity	% OS (x-yr)
HCVAD-Blina	Blinatumomab	38	37 (17-59)	100	97	85 (3-yr)
HCVAD-blina-inotuzumab	Blinatumomab and Inotuzumab	20	24 (18-47)	100	90	100 (1-yr)
GIMEMA LAL1913	Blinatumomab	149	41 (18-65)	90	96	84 (1-yr)
GRAALL-2014-Quest	Blinatumomab	95	35 (18-60)	NA	74	92 (1.5 yr)
Low-intensity-Blinatumomab	Blinatumomab	30	52 (39-66)	100	73	69 (2-yr)

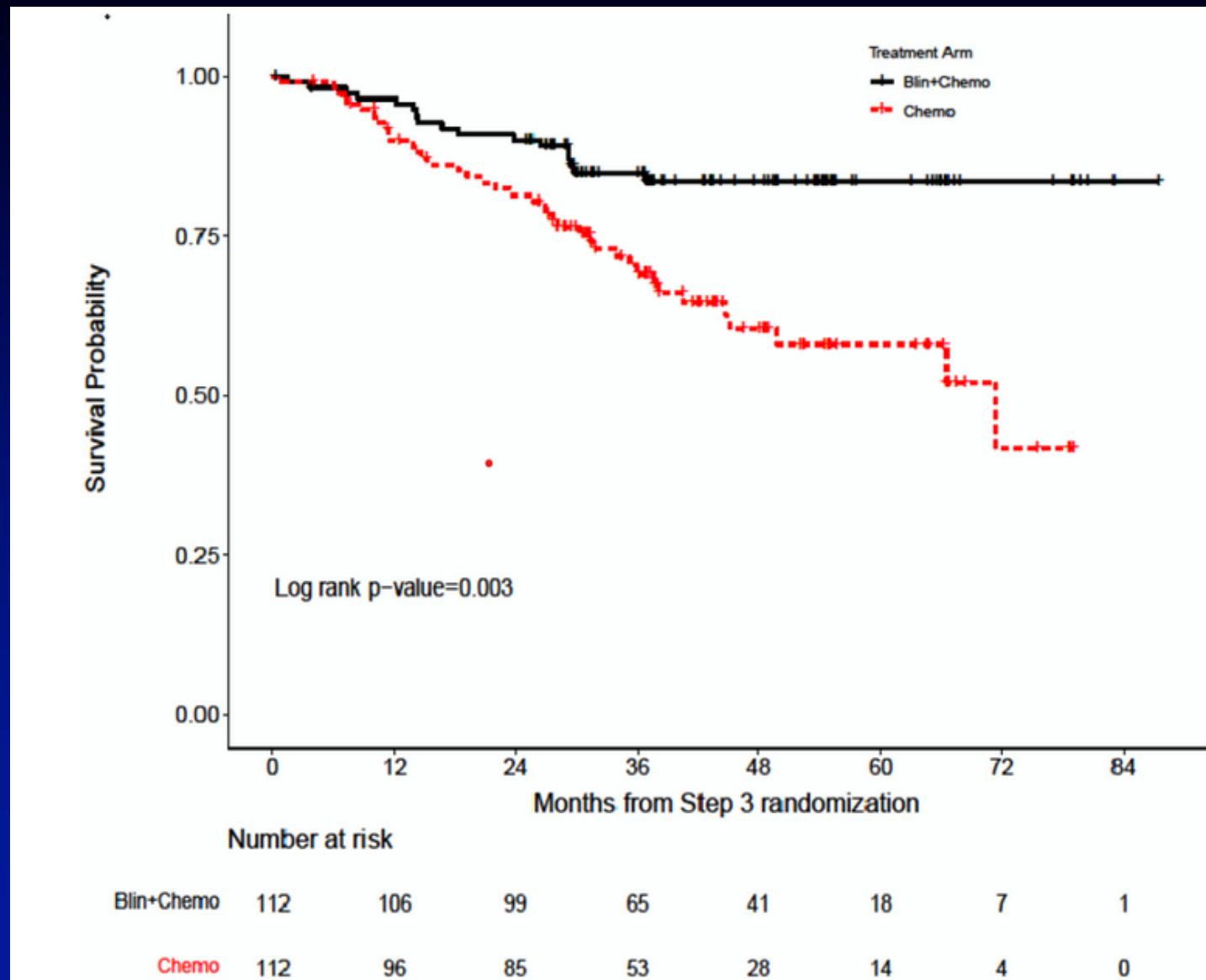
E1910: Randomized Phase 3 Trial: Blin vs SOC as Consolidation in MRD-Negative CR



- Accrual = 488
- US intergroup study
- n = 265/360 (509) patients
- USA, Canada, Israel
- 1:1 randomization

Adult Frontline ALL Rx-- E1910 Randomized Phase 3 Trial: Blin vs SOC Consolidation in MRD-Negative CR

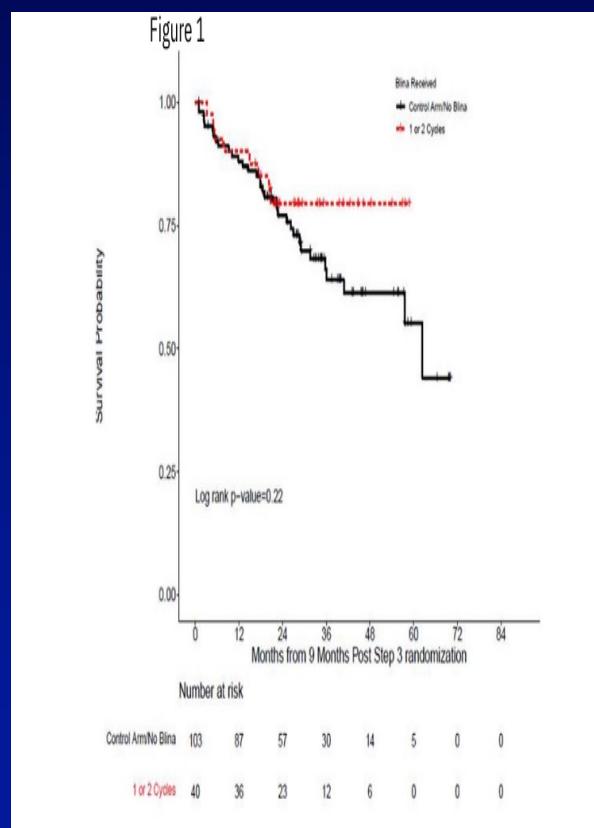
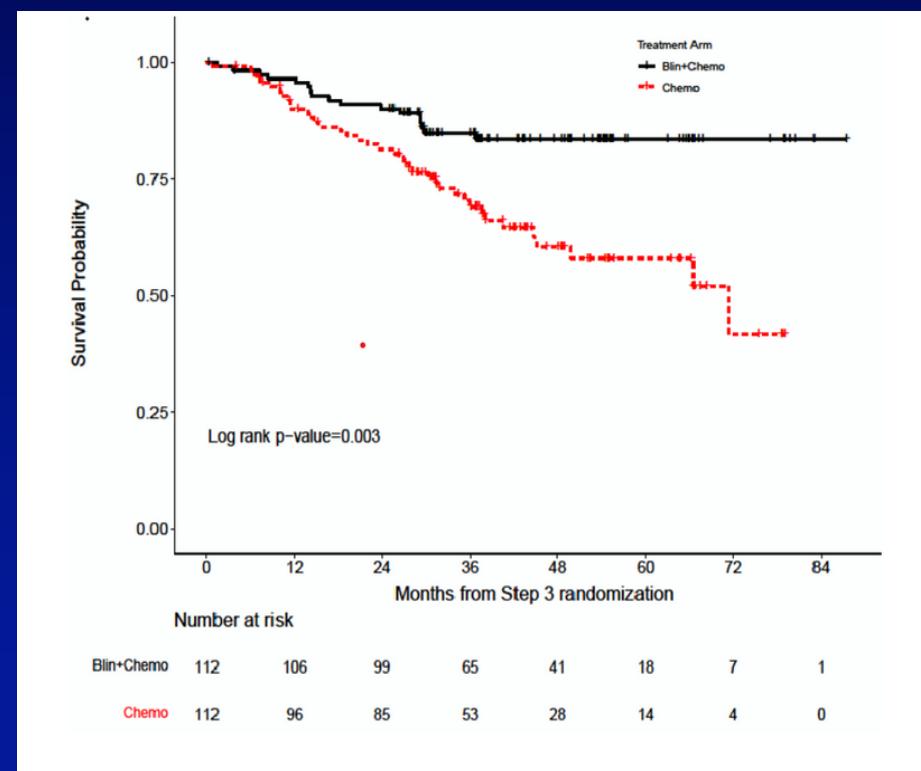
- 488 pts median age 51 yrs (30-70)
- 224 MRD-negative CR randomized 1:1 to blina vs SOC
- 22 pts (20%) had allo SCT in each arm
- Median F/U 43 mos; median OS NR vs 71.4 mos (HR=0.42; p=0.003)



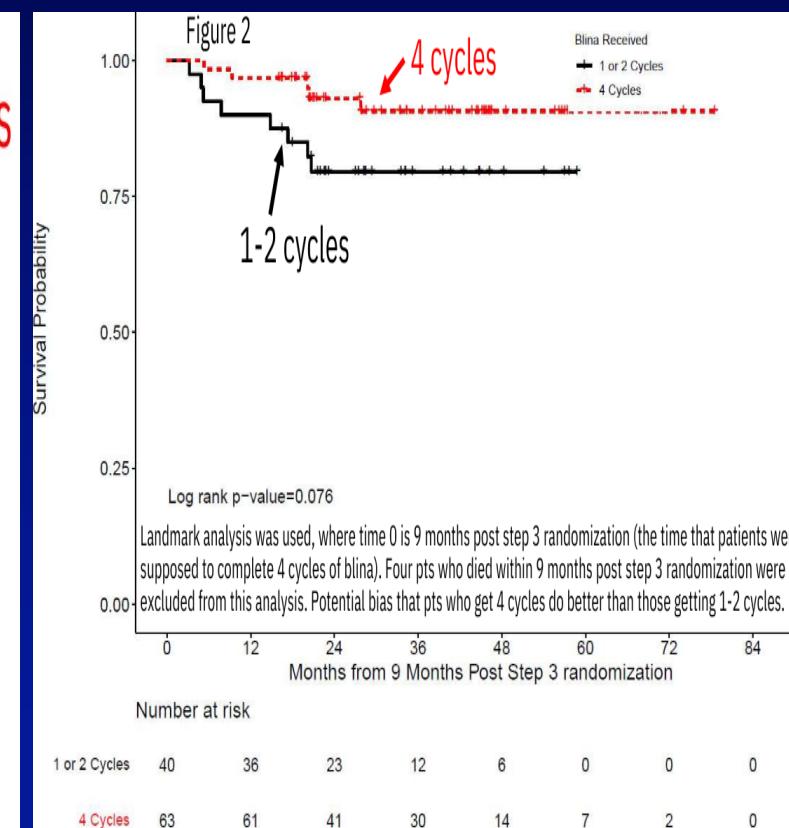
**How Many Courses of Blinatumomab is
Ideal?
2? 4-5? 7?**

E1910 Randomized Phase 3 Trial: Blina vs SOC Consolidation in MRD-ve. Outcomes by Number of Cycles

- 488 pts median age 51 yrs (30-70); median FU 43 mos
- 224 MRD-negative CR randomized 1:1
- Median OS NR vs 71.4 mos (HR=0.42; p=0.003); 5-yr OS 80% vs 55%
- No difference in OS trend if 1-2 courses of blina vs control (HR: 0.62; p=0.22)
- OS: 4 vs 2 courses (HR: 0.39; p=0.07). But 20% could not complete 4 courses due to blinatumomab toxicities

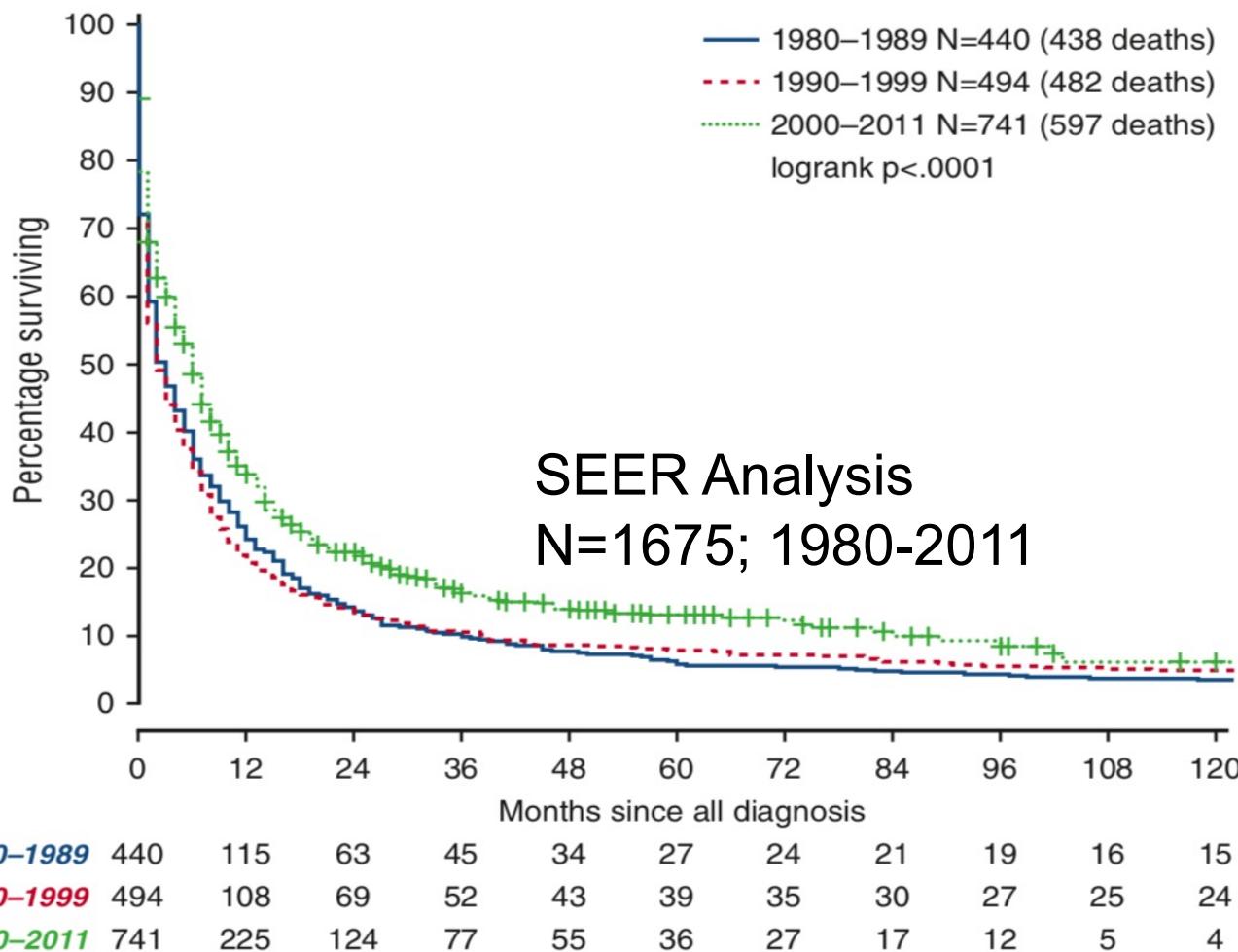


1 - 2 cycles
Vs
control



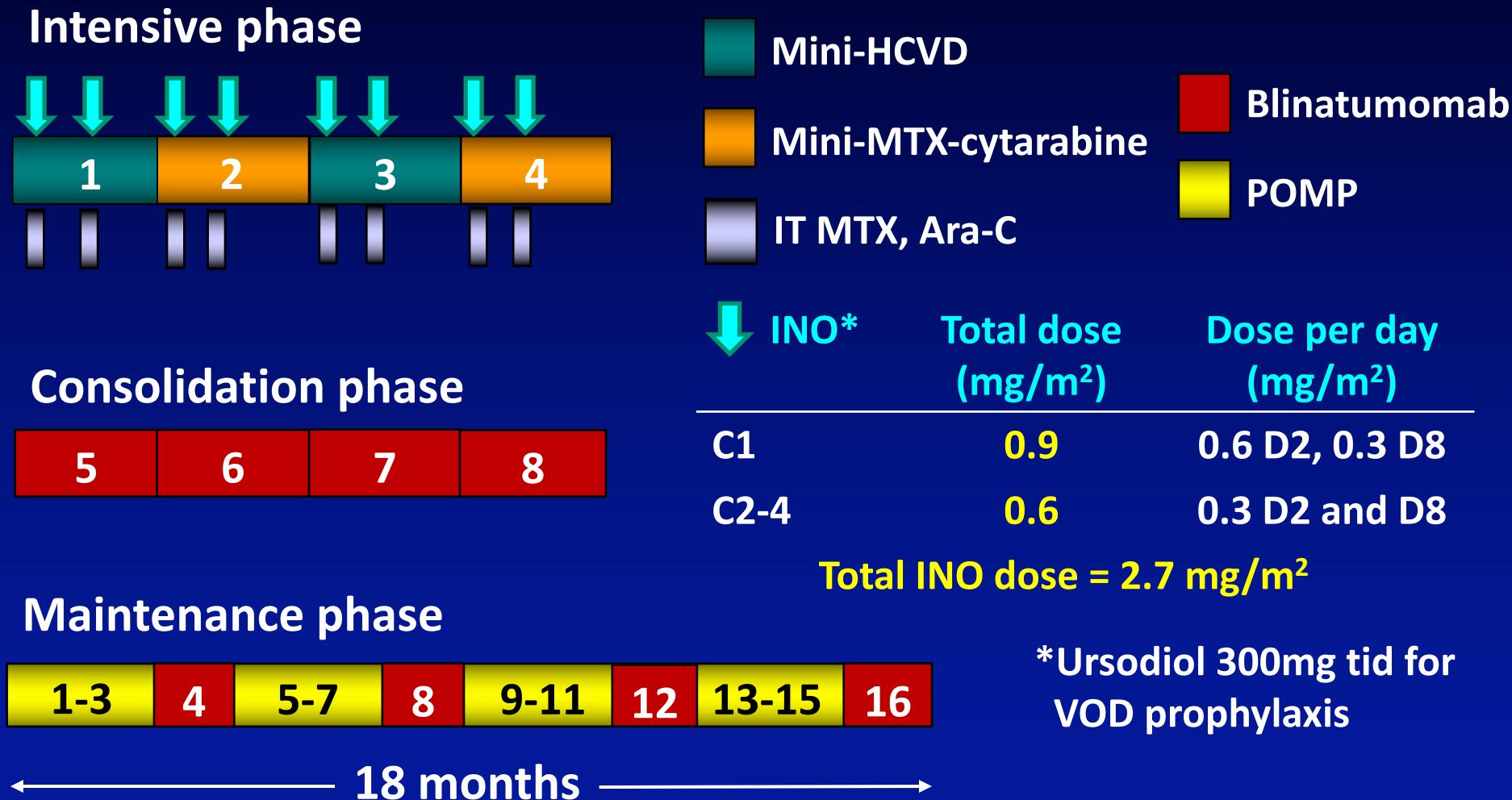
ALL in Older Adults: Historical Outcomes

Adults with ALL age ≥ 60 Yrs= minimal improvement over time



Population	3-year OS (%)	Median OS (months)
Overall	12.8%	4
Age (years)		
60-64	24%	9
≥ 75	10%	<3
Era		
Pre-1990	10%	3
2000-2011	16%	6

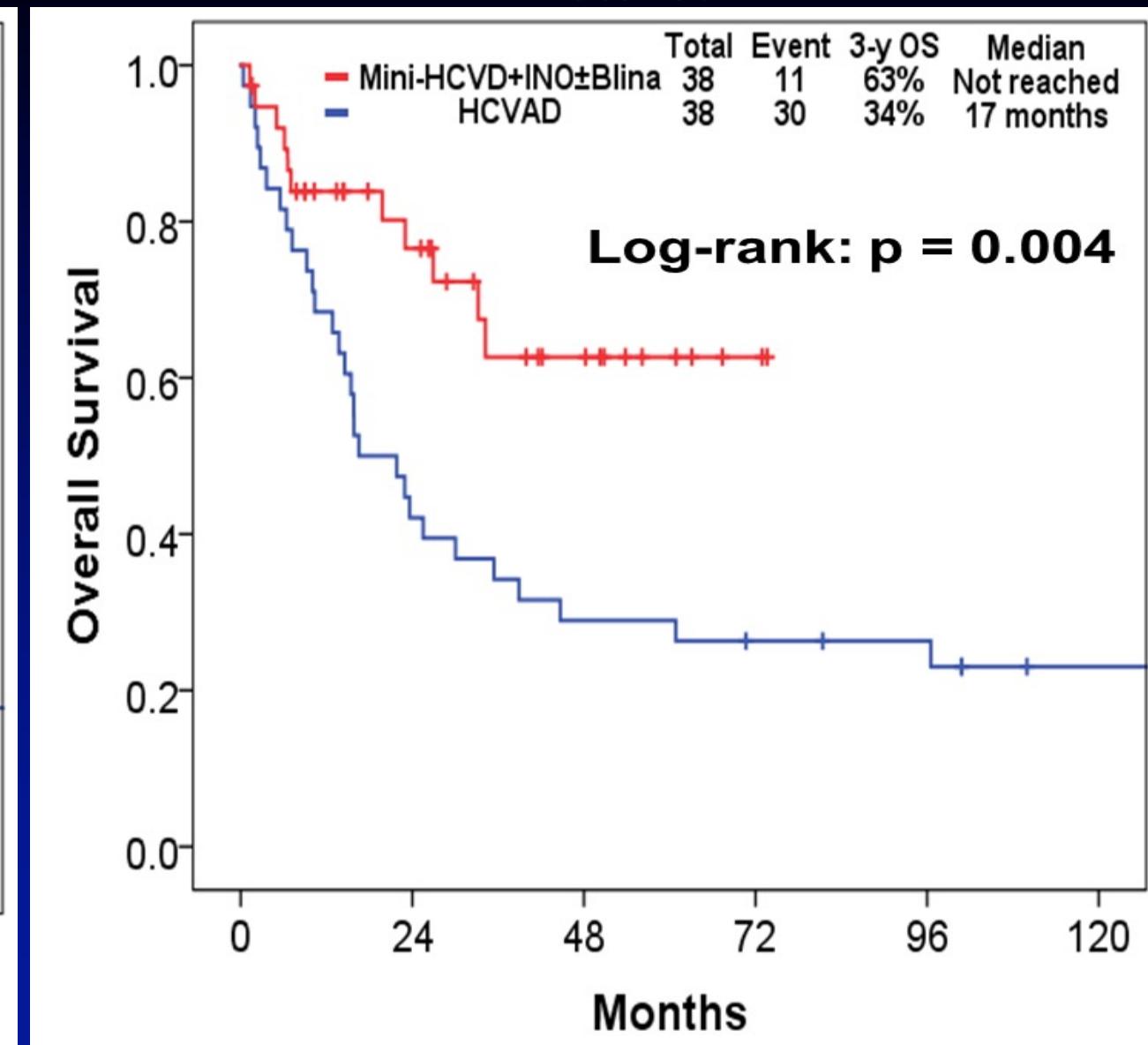
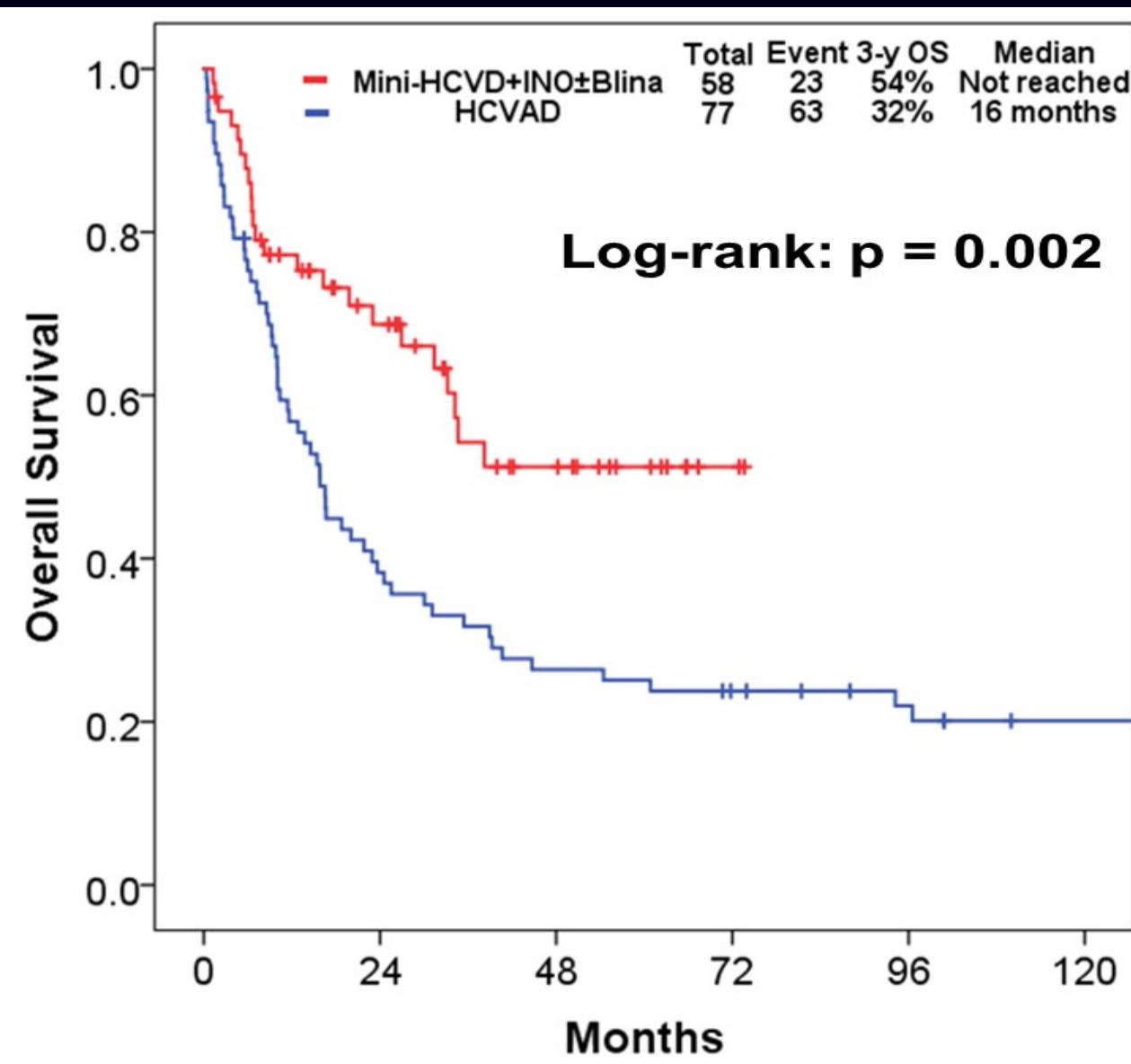
Mini-HCVD + Inotuzumab ± Blinatumomab in Older ALL: Modified Design (Pts #50+)



Mini-HCVD + INO ± Blina vs. HCVAD in elderly ALL. Survival

Pre-matched

Matched

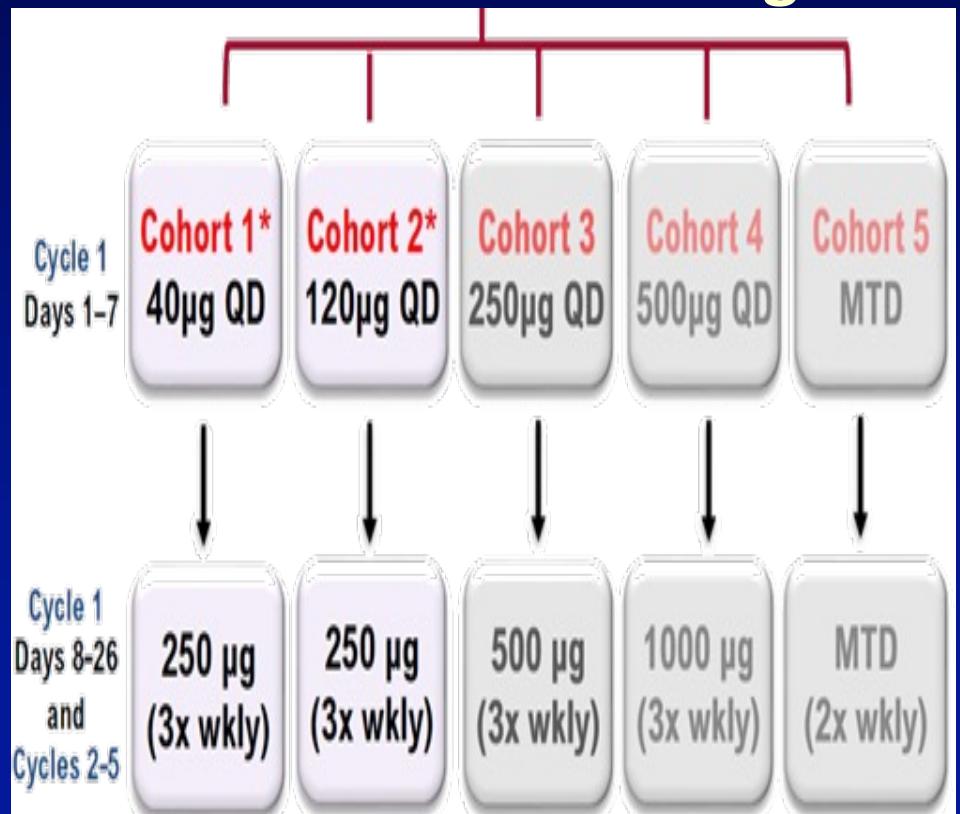


Frontline Blina and Inotuzumab Combinations in Newly Dx Older ALL

	Agent	N	Median Age (yrs, range)	% CR	% MRD negativity	% OS (x-yr)
Mini-HCVD-Inotuzumab-blinatumomab	Blinatumomab and Inotuzumab blinatumomab	79	68 (60-87)	89	94	55 (3-yr)
SWOG-1318	Blinatumomab	31	73 (66-86)	66	92	37 (3-yr)
EWALL-INO	Inotuzumab	131	69 (55-84)	88	57	54 (2-yr)
GMALL Bold	Blinatumomab	34	65 (56-76)	76	69	89 (1-yr)
INITIAL-1	Inotuzumab	45	65 (56-80)	100	74	81 (2-yr)
Alliance	Ino +Blin	33	71 (60-84)	97	--	67(2-yr)

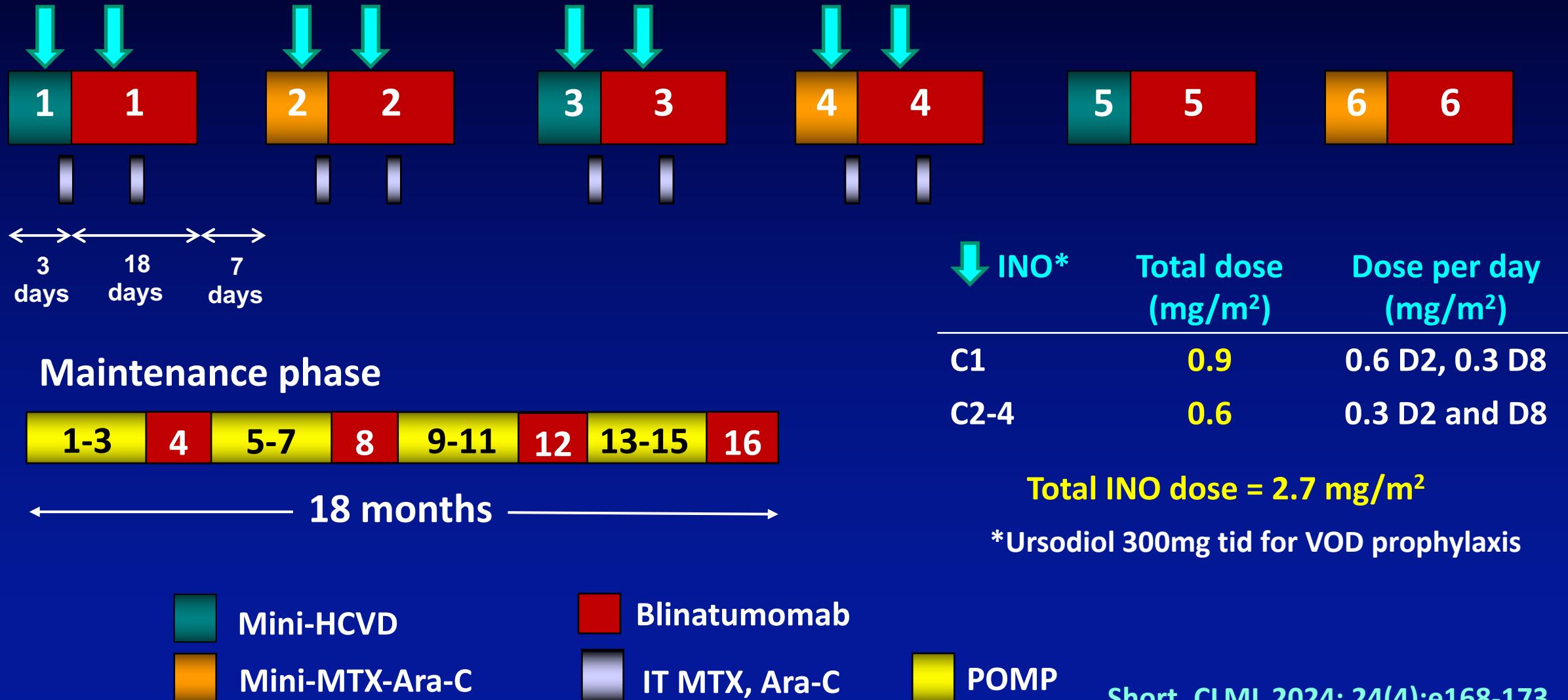
Subcutaneous Blinatumomab in R-R ALL

- 49 R/R pts – dose escalation 22, dose expansion 27
- BLINA 40, 120, 250, 500 mcg SQ daily x 7, then 250 mcg TIW in Cohorts 1 and 2 and 500 mcg in Cohort 3 and 1000 mg in Cohort 4
- G3 CRS 22%; G 3 CNS 22%
- Doses in Cohort 4 5x higher than IV BLINA



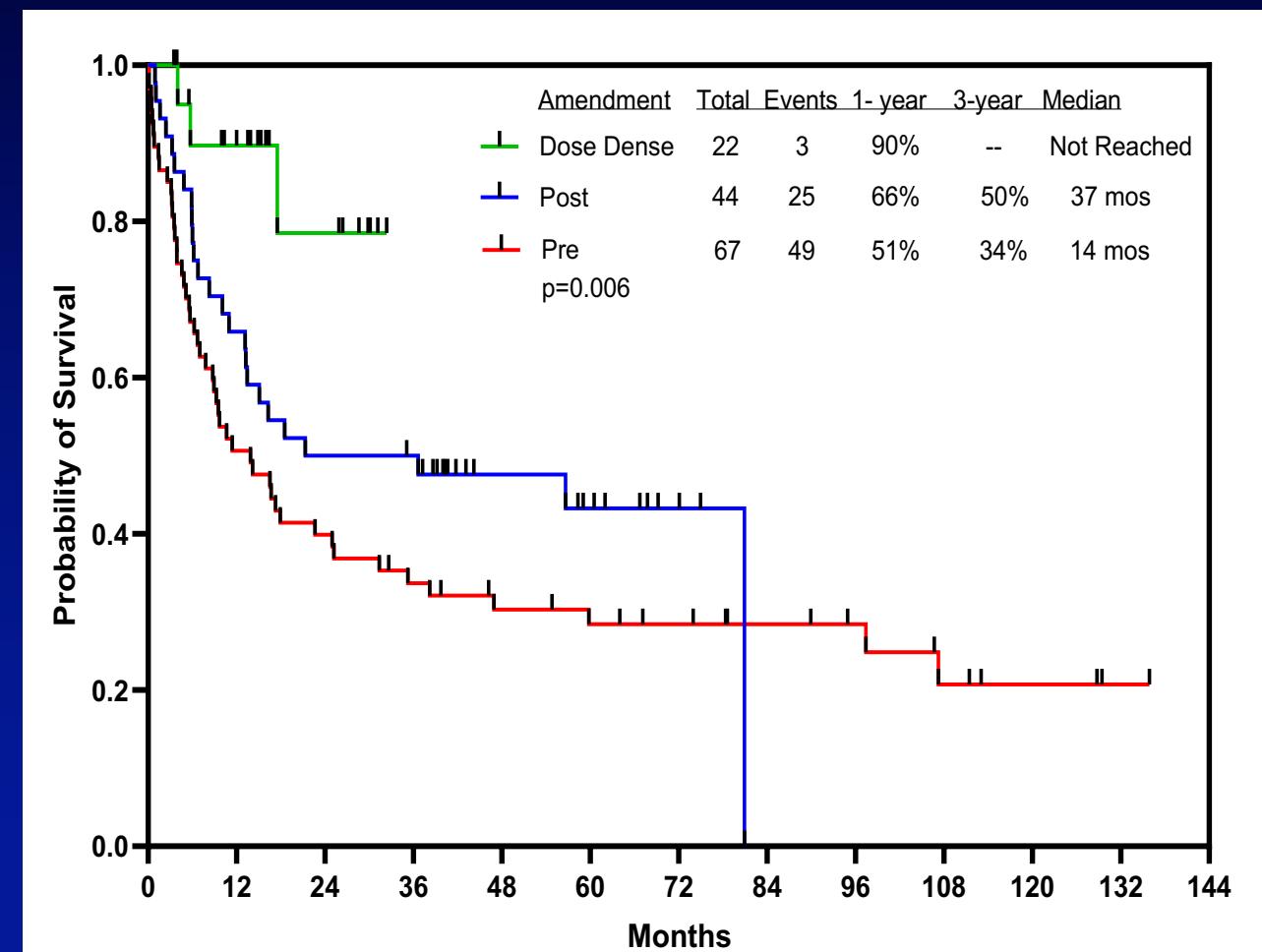
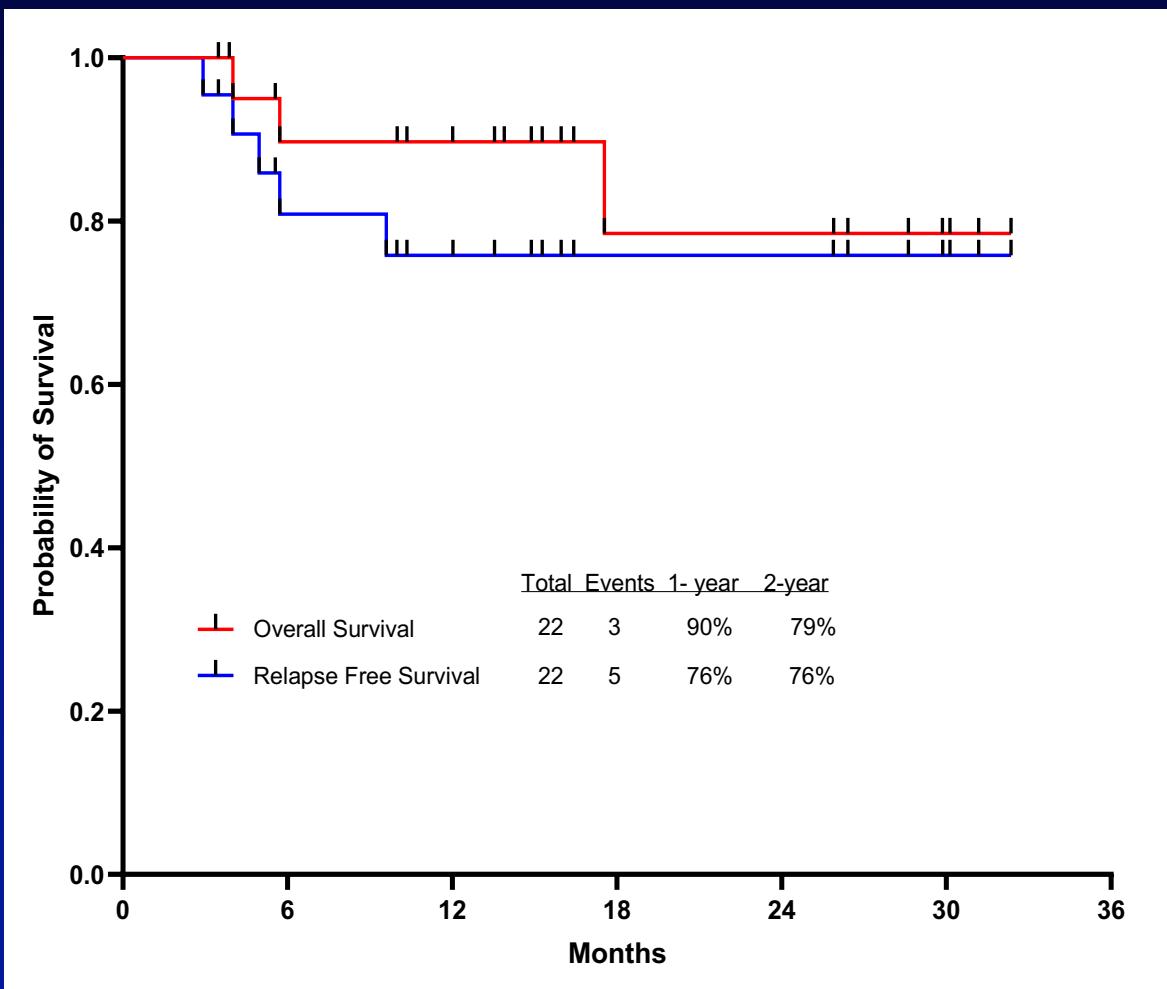
Cohort	Rx	% marrow CR	% MRD-negative
3 – 250/500	14	86	75
4 – 500/1000	13	92	100

Mini-HCVD + INO ± Blina in R/R B-ALL: “Dose-Dense” Design (Pts #111-125+)

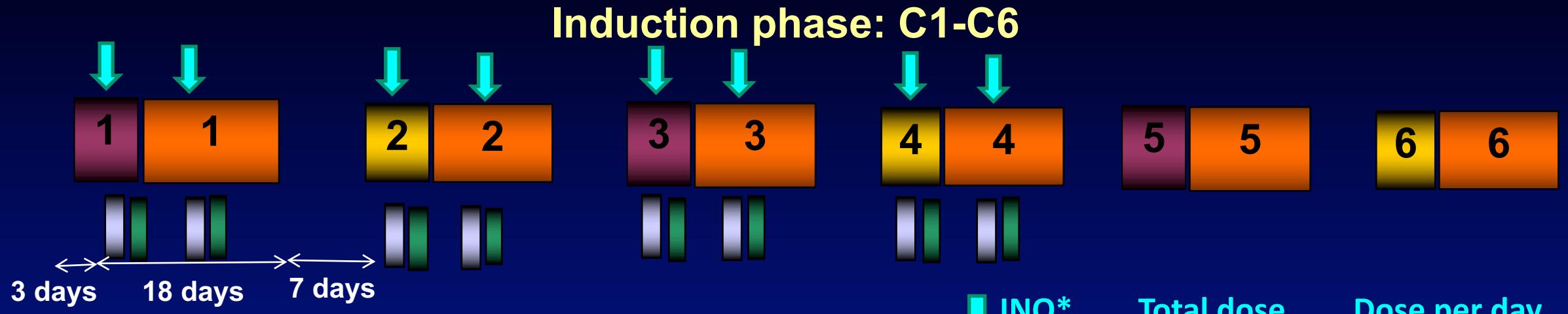


“Dose-Dense” Mini-HCVD + INO + Blina in R/R B-ALL.

- 22 pts median age 41 yrs (19-62) Rx; 86% S1
- ORR 100%--CR 81%; MFC-MRD negative 95% (74% after C1); NGS-MRD negative 94%
- Median F/U 15 months: 2-year OS 79%; 2-year RFS 76%



BRICK Regimen--Dose Dense Mini-HCVD + Inotuzumab + Blinatumomab (+/- CART) in ALL



Monitor MRD by NGS and decide

CAR T Consolidation

	Total dose (mg/m ²)	Dose per day (mg/m ²)
C1	0.9	0.6 D2, 0.3 D8
C2-4	0.6	0.3 D2 and D8

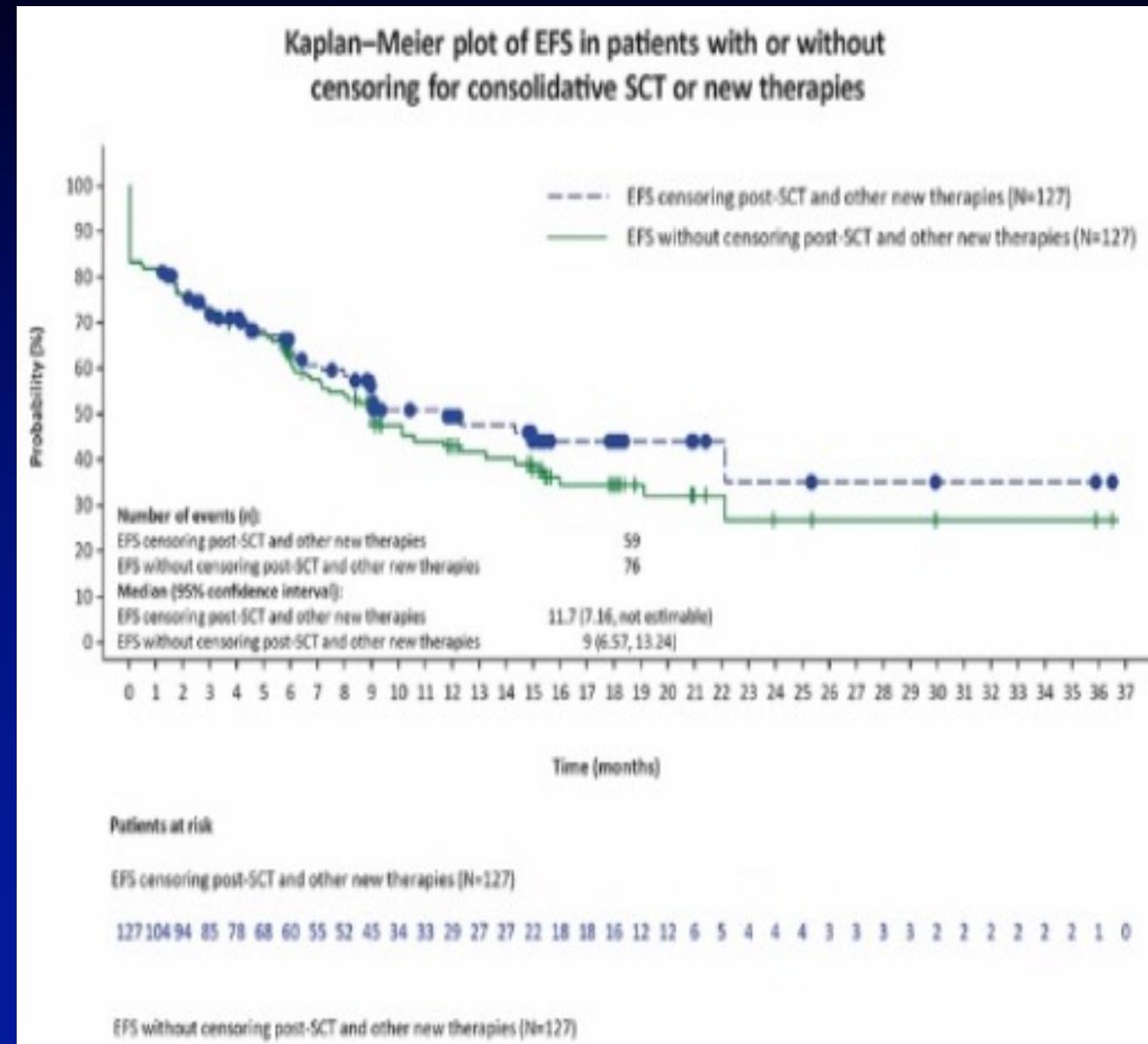
Total INO dose = 2.7 mg/m²

*Ursodiol 300mg tid for VOD prophylaxis



Obecaptagene Autoleucel (OBE-CEL) in Adult R-R ALL (FELIX)

- AUTO 1 fast off-rate CD19 binder CAR-T
- 153 enrolled, 127 (83%) infused. Median age 47 yrs
- G3 CRS 2.5%; G3 ICAN 7.5%
- Prior blina 42%, ino 31%, allo SCT 44%
- cCR-CRi 99/127 = 78% (99/153 = 65%). 19/77 allo SCT.
- Loss of CAR-T = HR 2.9
- 12-mos EFS 49%, 12-mos OS 61%



ALL – Summary

- Ph-positive ALL – Ponatinib-blinatumomab
- Antibody based Rxs and CARTs both outstanding. But uses different from FDA approvals
- Future of pre-B ALL Rx: 1) less chemotherapy for shorter durations; 2) combinations with ADCs and BiTEs/TriTEs targeting CD19, CD20, CD22; 3) CARTs in CR1 for MRD and replacing allo SCT;
- MRD by clonoseq/NGS
- SQ more potent and easily deliverable blinatumomab

Leukemia Questions?

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